American Journal of Obstetrics and Gynecology

VOL. 61 MAY, 1951 No. 5

Transactions of the Central Association of Obstetricians and Gynecologists. Eighteenth Annual Meeting Milwaukee, Wisconsin, September 21, 22, and 23, 1950

(Papers are presented in the order of their reading.)

THE PATHOGENESIS AND RELATIONSHIP OF THE HYALINE-LIKE PULMONARY MEMBRANE TO PREMATURE NEONATAL MORTALITY*†

PAUL D. BRUNS, M.D., AND LLOYD V. SHIELDS, M.D., DENVER, COLO.

(From the Department of Obstetrics and Gynecology, University of Colorado School of Medicine)

THE downward trend in infant deaths during the past quarter of a century has not kept pace with the tremendous drop in maternal mortality. Partially responsible for this tardiness are the many premature babies who die from little-understood causes in the first few days of life. It is generally concided that prevention of premature parturition would be one ideal way to decrease infant mortality. However, since the etiology of normal and premature labor is for the moment unknown, further investigations into the causes of premature neonatal deaths certainly are desirable and presently are being pursued with the hope of lowering existing infant mortality rates.

One of the pathological findings at autopsy in a considerable number of premature babies is the microscopic presence of a pulmonary hyaline-like membrane. Annually, in this country, it is estimated that between ten to twenty thousand premature infants who die within the first fortnight of life have a hyaline-like lining in their lungs. This pulmonary membrane is usually a homogeneous structure. It stains pink to red with hematoxylin-eosin dye and can be seen lining the alveoli, alveolar ducts, and bronchioles (Fig. 1).

*Presented at the Eighteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Milwaukee, Wis., Sept. 21 to 23, 1950.

†This work was aided by a grant from the Playtex Park Research Institute.

The histological characteristics of its formation have been described most thoroughly in the literature. Microscopically, this membrane has been associated with hyaline-like material lying loosely in the alveoli, aspirated amniotic sac contents, intra-alveolar fluid, hemorrhage, and infection. Its etiology, with few notable exceptions,[7, 19, 22, 43] has been assigned to aspiration of amniotic sac contents, chiefly vernix caseosa. Because of the accompanying pulmonary infection, its description in the literature oftentimes will be found under the title, "Pneumonia of the Newborn."[1, 2, 4, 8, 9, 10, 11] The clinical course of such infants dying with this pulmonary finding is sufficiently characteristic to warrant its accurate diagnosis.[43] At autopsy, its presence is frequently the only significant, discernible, pathological abnormality. Several authors have suggested, therefore, that hyaline-like membrane may be the primary cause of death in some newborn infants.[12, 20, 22, 43]

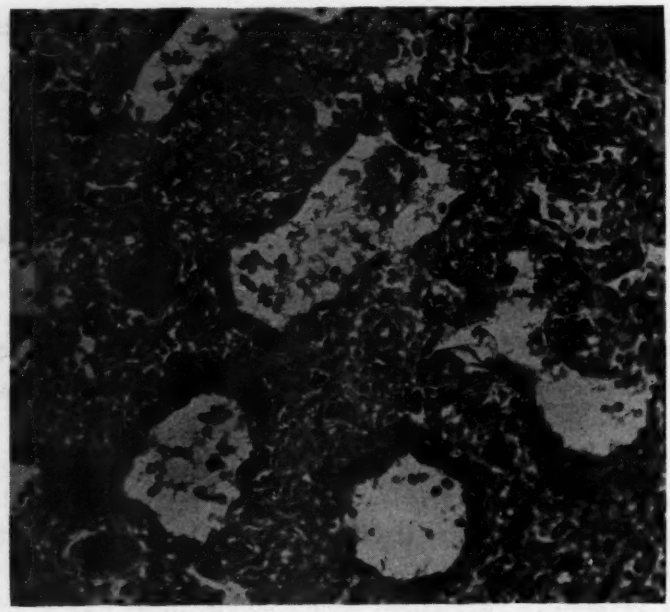


Fig. 1.—Hyaline-like membrane in the lung of a premature infant who died on the third neonatal day.

The Literature

The hyaline-like membrane in the lungs of infants has been described under the titles of asphyxial membrane, aspiration pneumonia, hyaline membrane, congenital pneumonia, vernix membrane, desquamative anaerosis, eosinophilic membrane, fibrinoid exudate or necrosis, and congenital alveolar dysplasia. Table I summarizes the literature on this membrane in infants. The major portion of investigative work has been done by intratracheal injection of foreign substances into the lungs of various laboratory animals. First such experiments[4] used lysol, soap solution, amniotic fluid, and egg albumin. One hyaline membrane was reported produced in a rabbit's lung by the latter protein. The second project[5] involved an extensive number and variety of animals, as well as foreign materials. India ink, horse serum, dilute hydrochloric acid, and fibrino-

purulent exudate were instilled, intratracheally, into animals subjected to artificial respiration (Drinker apparatus). Hyaline-like membranes, similar to those seen in influenza, were formed from the fibrinopurulent exudate in lungs of two living and two dead rabbits. In the third experimental approach to this problem,[21] warmed, centrifuged, amniotic fluid under positive and negative pressures was insufflated into heated lungs of several stillborn infants. Pseudo-hyaline-like membranes were produced under these circumstances. The most recent research,[22, 23] utilizing some 67 dogs and rabbits, failed to yield a hyaline-like membrane by the intratracheal introduction of vernix, meconium, amniotic fluid, saline, Ringer's lactate solution, and distilled water. The latest theory concerning its formation, advanced by Miller and Jennison,[43] states, "The hyaline-like material in the lung is the result of an etiologic agent that not only injures the lungs of the fetus, but also causes the premature birth of the infant."

TABLE I. SUMMARY OF LITERATURE

YEAR	AUTHOR	CASES	SUGGESTED ETIOLOGY	RESEARCHES
1903	Hochheim	2	Aspiration, metabolic change	43 Autopsies
1923	Johnson	4	Aspiration, irritation	4 Case histories
1925	Johnson, Meyer	8	Aspiration amniotic fluid	500 Autopsies (Rabbits)
1928	Hook, Katz	1	Aspiration, irritation	73 Autopsies
1931	Farber, Sweet	18	Aspiration Amniotic contents	124 Autopsies
1932	Farber, Wilson	50	Aspiration, mechanical dispersion	(Rabbits, cats, dogs, rats)
1933	Rutledge	2	None	42 Autopsies
1933	Helwig	2	Aspiration amniotic fluid	159 Autopsies
1935	Rosenthal	31	Degeneration and desquamation	100 Autopsies
1937	Steinharter	3	Aspiration, mechanical dispersion	Study of cases
1939	Macgregor	11	Aspiration, mechanical dispersion	541 Autopsies
1940	Benner	2	Aspiration, infection	70 Autopsies
1942	Ahlstrom	5	Aspiration, condensation	27 Autopsies
1946	Russ	9	Aspiration amniotic contents	137 Ces. sect. with 12 infant deaths
1947	Schenken	32	Aspiration amniotic fluid	80 Autopsies
1947	Arey	4	Aspiration amniotic contents	22 Autopsies
1947	Labate	4	Aspiration, absorption	868 Autopsies
1947	Ahvenainen	42	Aspiration, desquamation	108 Autopsies
1948	MacMahon	3	Developmental anomaly	3 Case histories
1949	Dick, Pund	7	Aspiration, absorption, dispersion	119 Autopsies (stillborns)
1949	Miller, Hamilton	26	Capillary and epithelial injury	79 Necropsies (dogs and rabbits)

A similar membrane has been described in the lungs of children and adults in a number of clinical pathologic states. Likewise, it has been produced in numerous experimental animals by chemical, physical, immunologic, and bacterial agents. Table II summarizes a number of these diversified factors. The concepts regarding the etiology of these hyaline-like membranes are based primarily on pulmonary capillary and epithelial damage. The mechanism by which this injury is accomplished includes direct contact agents, circulating toxins, focal anaphylactic reactions and intercapillary thrombosis.

The frequency with which the hyaline-like membrane has been encountered in neonatal deaths of premature infants varies from a low of 2.5 per cent, reported by Macgregor,[10] to a high of 50 per cent, published by Ahvenainen[20] and Miller and Hamilton.[22]

TABLE II. CLINICAL AND EXPERIMENTAL CONDITIONS WHERE HYALINE-LIKE MEMBRANES HAVE BEEN DESCRIBED

Radiation pneumonitis	Warren and Gates	Arch. Path. 30: 440, 1940.
Influenzal pneumonia	Wolbach	Bull. Johns Hopkins Hosp. 30: 104, 1919.
Aspiration of amniotic contents	Johnson and Meyer	AM. J. OBSTET. & GYNEC. 9: 151, 1925.
War gases and HCl	Winternitz	Path. War Gas Poisoning, New Haven, 1920, Yale University Press.
Rheumatic pneumonitis	Neuberger, Geever, Rutledge	Arch. Path. 37: 1, 1944.
Sulfonamide anaphylactic pneumonitis	Rich and Gregory	Bull. Johns Hopkins Hosp. 73: 465, 1943.
Plague	Strong, Crowell, Teague	Philippine J. Sc. 7: 203, 1912.
Septicemia and chronic infection	Brannon and Goodpasture	Arch. Int. Med. 34: 739, 1924.
Atypical pneumonia Metatastic chorionepithelioma Acute and chronic glomerular nephritis	Neubuerger	Unpublished, Dept. Pathology, University of Colorado.
Oxygen poisoning	Kuhn and Pichotka	Arch. f. exper. path. u Pharmakol. 205: 667, 1948.
Cadmium chloride aerosol	Harrison et al.	J. Indust. Hyg. & Toxicol. 29: 302, 1947.
Oxides of nitrogen	Mallory and Brickley	Ann. Surg. 117: 865, 1943.

Material

The statistics concerning the hyaline-like membrane used in this study were compiled from a review of the clinical histories, protocols, and microscopic slides of all stillborn infants and infants who died in the neonatal period at Colorado General Hospital, from July 1, 1939, through June 30, 1950, and at Denver General Hospital, from Jan. 1, 1947, through June 30, 1950. Infants born at other hospitals, but autopsied at Colorado General Hospital were included in the study. During the combined period of 14½ years, there were 10,896 births resulting in 10,397 living children, 267 infants who died in the neonatal period, and 232 stillborn infants. A total of 740 autopsies on fetuses was performed. Of these, 298 were autopsies of infants born at other hospitals, 295 at Colorado General Hospital and 147 at Denver General Hospital. Of the total autopsy number, there were 456 neonatal deaths and 284 stillborn infants. Microscopic slides were available for necropsies performed on 439 infants who died neonatally and 264 stillborn infants, making a total of 703, among which were found 114 cases of hyaline-like pulmonary membrane. This represents a total autopsy frequency of 16.2 per cent. The occurrence of the membrane at autopsy in cases of neonatal death in this study was 25.9 per cent (Table III). The breakdown for the various weight groups covered a span of 6 to 44 per cent. The highest incidence occurred in the birth weight category of 1,000 to 1,500 grams (Table IV).

Maternal and infant histories from the University Hospitals, together with autopsy protocols and microscopic sections, were available for only 62 of the

114 infants with hyaline-like membrane. The detailed analysis made in this study is based upon these 62 infants and their mothers from Colorado and Denver General Hospitals (Table V).

TABLE III. INCIDENCE OF HYALINE-LIKE MEMBRANE IN AUTOPSY MATERIAL FROM THE UNIVERSITY OF COLORADO DEPARTMENT OF MEDICINE
(COLORADO GENERAL HOSPITAL, JULY, 1939, THROUGH JUNE, 1950)
(DENVER GENERAL HOSPITAL, JANUARY, 1947, THROUGH JUNE, 1950)

Fetal autopsies with available microscopic sections	703
Neonatal deaths with available microscopic sections	439
Stillborn infants with available microscopic sections	264
Total number of hyaline-like membranes	114
Autopsy incidence of hyaline-like membranes	16.2%
Autopsy frequency of hyaline-like membrane in deaths of newborn infants	25.9%

TABLE IV. INCIDENCE OF HYALINE-LIKE MEMBRANE IN LUNGS OF INFANTS WHO DIED IN THE NEONATAL PERIOD
(COMBINED SERVICES OF COLORADO AND DENVER GENERAL HOSPITALS, 1946-1950)

BIRTH WEIGHT IN GRAMS	TOTAL BIRTHS	STILL BORN	LIVED	DIED	NUMBER OF HYALINE-LIKE MEMBRANES IN INFANTS WHO DIED IN THE NEONATAL PERIOD	PERCENTAGE OF HYALINE-LIKE MEMBRANES IN INFANTS WHO DIED IN THE NEONATAL PERIOD
500- 999	109	52	6	51	4	8
1,000-1,499	94	21	37	36	16	44
1,500-1,999	170	10	135	25	10	40
2,000-2,499	439	17	400	22	6	27
2,500 or over	4,918	47	4,835	36	2	6
Total	5,730	147	5,413	170	38	22

No hyaline-like membranes were found in stillborn infants.

TABLE V. SIXTY-TWO CASES OF HYALINE-LIKE MEMBRANE WITH COMPLETE HISTORIES AND PATHOLOGIC STUDY IN 239 NEONATAL DEATHS
(COMBINED SERVICES OF COLORADO AND DENVER GENERAL HOSPITALS, 1939-1949)

BIRTH WEIGHT	HYALINE-LIKE MEMBRANES IN NEONATAL DEATHS	
	NUMBER	PER CENT
500- 999	5	8.1
1,000-1,499	22	35.5
1,500-1,999	19	30.6
2,000-2,499	10	16.1
2,500 or over	6	9.7
Total	62	100

Autopsy frequency in deaths of newborn infants, 25 per cent.

Experimental Procedure

A preliminary experiment was carried out on three adult and nine infant guinea pigs. These animals all were placed in an oxygen chamber containing 98 per cent oxygen at 760 mm. Hg pressure. Temperature and humidity were not rigidly controlled, but remained near 25° C. and 50 per cent relative humidity. All animals were provided food and water and were kept in the oxygen chamber until death occurred spontaneously.

Guinea pig No. 1 was an adult male which died spontaneously in oxygen after 64 hours. The lungs from this animal showed the presence of a hyaline-like membrane. Guinea pig No. 2 was an adult in early pregnancy which died spontaneously in oxygen after 50 hours. Immediately following death, a post-

mortem cesarean section was done, yielding two dead fetuses. In this case, the mother's lungs were positive for hyaline-like membrane, while the lungs of each of her fetuses were microscopically normal. The third animal, an adult guinea pig in late pregnancy, aborted two fetuses after 32 hours in oxygen and then died spontaneously in oxygen 10 hours later. One of these abortuses was destroyed by the mother. The other was removed from oxygen immediately after birth and killed. The mother's lungs showed hyaline-like membrane formation, while the lungs of the remaining aborted fetus were normal.

Two 3-day-old guinea pigs remained in oxygen 38 and 151 hours, respectively. The lungs of both of these young animals revealed a hyaline-like membrane. Of four 1-day-old guinea pigs, only one had a hyaline-like membrane, while its presence in another was doubtful.

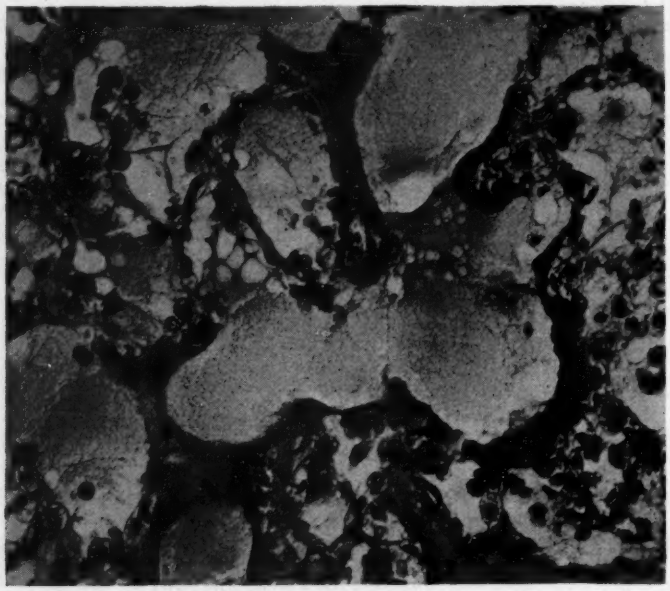


Fig. 2.—Hyaline-like membrane in the lung of a pregnant adult guinea pig which died after exposure to 98 per cent oxygen for 50 hours.

The results of this pilot study revealed the method of membrane production to be simple and satisfactory. It was possible to produce a hyaline-like membrane in six out of nine animals whose lungs were directly exposed to high concentrations of oxygen at sea level pressure. It should be noted that none of the intrauterine fetuses of the two experimental, pregnant guinea pigs showed evidence of pulmonary, hyaline-like membrane. Fig. 2 demonstrates the similarity of the experimentally-produced membrane to the ones found in lungs of prematures who died in the early neonatal period. The general pathological findings in all animals which died in high concentrations of oxygen were paradoxically those of anoxia. Table VI gives the results of this preliminary work.

The Maternal Study

A review of the maternal aspects of this study tends to confirm previous reports[20, 43] that parity, age, race, serology, rhesus factor, analgesia, anesthesia, maternal and obstetrical complications, and type of delivery bear no direct relationship to the formation of a hyaline-like membrane (Tables VII and VIII). One-third of the mothers in this series delivered prematurely without apparent

TABLE VI. TWELVE GUINEA PIGS KEPT IN 98 PER CENT OXYGEN AT 760 MM. HG ATMOSPHERIC PRESSURE

GROUP	NUMBER	ANIMAL	TYPE OF DEATH	HOURS IN O_2	HYALINE-LIKE MEMBRANE
I	1	Normal adult male	Spontaneous in oxygen	64	Positive
II	2	Normal pregnant adult (early pregnancy)	Spontaneous in oxygen	50	Positive
		Fetus A from animal No. 2	Delivered post mortem. Died in utero	--	Negative
		Fetus B from animal No. 2	Delivered post mortem. Died in utero	--	Negative
	3	Normal pregnant adult (late pregnancy)	Spontaneous in oxygen	42	Positive
		Fetus A from animal No. 3	Delivered spontaneously in oxygen. Killed	--	--
		Fetus B from animal No. 3	Delivered spontaneously in oxygen. Killed	--	Negative
III	4	3-day-old guinea pig	Spontaneous in oxygen	38	Positive
	5	3-day-old guinea pig	Died after 2 hours in air	151	Positive
IV	6	1-day-old guinea pig	Spontaneous in oxygen	38	Positive
	7	1-day-old guinea pig	Spontaneous in oxygen	79	Negative
	8	1-day-old guinea pig	Spontaneous in oxygen	107	Negative
	9	1-day-old guinea pig	Spontaneous in oxygen	119	Doubtful

TABLE VII. TABULATION OF THE MATERNAL FACTORS FROM 56 MOTHERS WHOSE 62 LIVEBORN INFANTS HAD HYALINE-LIKE MEMBRANE FORMATIONS IN THE LUNGS

		NUMBER
Parity	Primipara	15
	Multipara	37
	Unknown	4
Age	Varied from 14 to 39 years	
Race	White	40
	Spanish-American	10
	Negro	6
Serology	Positive	1
Rhesus Factor	Negative, not sensitized	1
Prenatal care	Yes	33
	No	16
	Unknown	7
Analgesia and amnesia	None	26
	Morphine and like drugs	15
	Barbiturates	14
	Scopolamine	6
Anesthesia	None	13
	Pudendal block	22
	Inhalation anesthesia	18
	Spinal	5

TABLE VIII. MATERNAL AND OBSTETRICAL COMPLICATIONS, TYPE OF DELIVERY, AND GROSS AUTOPSY FINDINGS IN 62 INFANTS WITH HYALINE-LIKE MEMBRANE

MATERNAL AND OBSTETRICAL COMPLICATIONS	NUMBER	TYPE OF DELIVERY	NUMBER	GROSS AUTOPSY FINDINGS	NUMBER
None	23	Spontaneous	32	None	25
Multiple pregnancy	13	Low forceps	10	Hemorrhage, brain	25
Toxemia	12	Breech extraction	10	Hemorrhage and laceration, brain	9
Infection	11	Cesarean section	10	Malformations	2
Hemorrhage	8			Hemorrhagic disease	1
Other	8				

cause, while maternal complications which predispose to or are associated with prematurity occurred in two-thirds of the cases. The type of delivery, such as breech extraction and cesarean section, was that usually employed for such obstetrical conditions as multiple pregnancy, toxemia, and antepartum hemorrhage. Likewise, duration of labor, time of rupture of the membranes, and maternal administration of sulfonamides and antibiotics showed no pattern of significance in relation to the occurrence of hyaline-like membrane in the infant.

Infants' Histories

Resuscitative procedures exercised on the newly born infants in this study varied widely, depending upon the methods and materials in vogue (Table IX). Aspiration of the nasopharynx with the rubber catheter and bulb usually took precedence over intratracheal suction and postural drainage. There were 18 infants who did not have aspiration of the respiratory trees by any technique. No definite patterns of resuscitation were used on these infants. Forty-one of the 62 babies required no artificial resuscitative measures whatsoever, and in those remaining the techniques were numerous enough to preclude any one as an etiological factor. The only therapeutic agent apparently used on nearly all of these infants involved the administration of oxygen. From the 62 histories, no reference could be found as to whether five of these babies received any oxygen in the neonatal period. Since it is the policy of this hospital, as well as most others, to place premature infants in oxygen immediately after birth, it would seem that the figure for the percentage of cases in which oxygen was employed should be closer to 100 per cent than to the 92 per cent recorded.

TABLE IX. THE RESUSCITATIVE MEASURES EMPLOYED ON 62 INFANTS WITH HYALINE-LIKE MEMBRANE

		NUMBER	PER CENT
Aspiration	None	18	29
	Nasopharyngeal	34	55
	Intratracheal	10	16
Resuscitation	None	41	66
	Positive pressure	8	13
	Mouth to mouth	5	8
	Other artificial methods	8	13
Gases employed	None	5	8
	Oxygen	55	89
	Oxygen and carbon dioxide	2	3
Drugs used	Vitamin K	31	50
	Caffeine	24	39
	Coramine	13	21
	Vitamin C	10	16
	Other drugs	23	

The clinical syndrome of the infants, from birth to death, in this study and from other reports followed a rather uniform pattern. At the time of birth, the premature baby was reported to be in poor condition. After he was placed in oxygen, the dyspnea and cyanosis which were present at birth were temporarily ameliorated. However, all of these infants continued to have difficulty breathing even in oxygen, showing costal retraction, periods of apnea and cyanosis. They died within 3 to 87 hours after birth.

The amount of hyaline-like membrane found on microscopic section was graded rather arbitrarily from one to four plus. In only 10 per cent of the 62 cases was the maximum grade attained. Fig. 3 attempts to correlate the amount of this membrane to the birth weight and duration of life. Even with this small number of cases, there seems to be a tendency to increased membrane

formation with the advancing hours of life and the increased birth weights. In 703 autopsies, no hyaline-like membrane could be found in the lungs of stillborns. The gross autopsy findings were nonrevealing in 25 infants and were nothing more than those associated with anoxia in another 25. An adequate pathologic cause of death could be found in only 12 cases. Moderate to severe cerebral hemorrhage, associated with tears of the falx or tentorium, occurred in 9 infants while malformations (coarctation of the aorta and esophageal atresia), accounted for two. The remaining infant succumbed with hemorrhagic disease of the newborn. It is worth noting that in 50 of the autopsy protocols of the hyaline-like membrane cases, atelectasis was tabulated as one of the chief causes of death. In this series, a left-sided pneumothorax was associated with one infant's death which had been assigned to atelectasis.

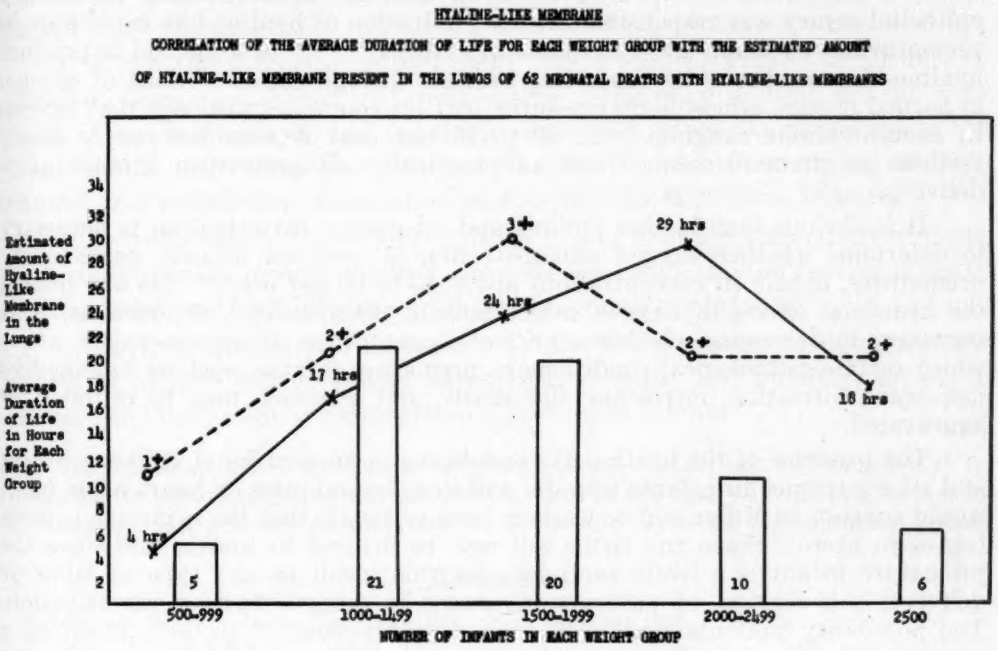


Fig. 3.

Comment

Following Miller, Hamilton, and Jennison's work,[22, 43] it seems reasonable to conclude that the pathogenesis of the hyaline-like membrane in the lungs of prematures is not due to aspiration of amniotic sac contents. Their suggestion that its etiology represents a reaction to pulmonary epithelial injury is indorsed by the results of this study. These authors likewise ascribe the cause of premature birth to the same agent which causes injury to the infant's lungs. This latter proposition is most interesting and certainly deserves further investigation. Obstetricians might approach the problem of premature labor by a coordinated project which would study simultaneously in a single patient the mechanical, chemical, vascular, endocrine, and nervous patterns of uterine growth and motility.[45]

In experiments on guinea pigs and rabbits, Pichotka and Kuhn[39] investigated the morphological changes in the lungs following high concentrations of oxygen (85 to 98 per cent) at reduced, normal, and high atmospheric pressures.

At reduced total pressures (200 mm. Hg), the animals showed no clinical or morphological changes. At normal and high atmospheric pressures (760 mm. Hg and over), the animals died showing considerable lung damage. Of particular interest were the histological findings of hyaline-like membranes in the alveoli, alveolar ducts, and bronchioles. These investigators concluded, on the basis of clinical, gross, and microscopic findings, that the cause of death in oxygen poisoning of this subacute or chronic variety (over 48 hours) was essentially one of anoxia.

It should be stated at the outset that the preliminary experiment described in this study was designed to determine the feasibility and reproducibility of a hyaline-like membrane in the lungs of guinea pigs. The reasons for selecting this avenue to the study of hyaline-like membranes were: (a) Miller and co-workers, suggestion[22, 43] that an unknown etiologic agent causing pulmonary epithelial injury was responsible for the production of hyaline-like membrane in prematures; (b) Kuhn and Pichotka's description[39, 40, 42] of a method to produce hyaline-like membrane by subjecting animals to high concentrations of oxygen at normal or high atmospheric pressures; (c) the common knowledge that oxygen in concentrations ranging from 30 to 95 per cent is administered to many mothers in premature labor and to practically all premature infants after delivery.

It is obvious that further clinical and laboratory investigation is necessary to determine whether oxygen administration to newborn infants, particularly prematures, is safe in concentrations above 40 to 60 per cent.[47] No one doubts the beneficial effects of oxygen inhalations in therapeutics; nevertheless, it is necessary to determine whether a critical concentration of oxygen exists, above which certain pathological conditions in premature infants, such as hyaline-like membrane formation, retrolental fibroplasia, and sclerema, may be initiated or aggravated.

The presence of the hyaline-like membrane in an occasional stillborn infant and its occurrence in infants who die within a few minutes or hours after birth would suggest, as Miller and co-workers have reported, that the injurious process begins in utero. Since any tissue cell may be injured by anoxia and since the premature infant is a likely candidate for this insult in any type of labor or delivery, this concept of pathogenesis seems to deserve further investigation. The possibility presents itself that high concentrations of oxygen, given to a premature in the immediate neonatal period, may further injure tissue to the extent of producing the above-mentioned diseases.

In the past, multiple numbers of histological stains have been employed to determine the nature and composition of the hyaline-like membrane. Except to show that some membranes contain fat and others not, or that the membrane is not composed of fibrin or collagen, this approach to the problem has not been especially rewarding. Perhaps biophysical techniques, utilizing electrophoresis and ultracentrifugation, may aid in establishing the exact nature of hyaline-like material in the lungs of infants.

It is of some interest that the hyaline-like pulmonary membrane was found histologically in a majority of the cases anatomically diagnosed as atelectasis. Many will agree that the latter diagnosis contributes little to the understanding of fetal pathologic conditions. Undoubtedly in many cases which have been diagnosed anatomically as atelectasis, there was a well-developed hyaline-like membrane in the lungs. Perhaps the autopsy diagnosis of atelectasis is too inclusive and under certain circumstances the hyaline-like membrane formation should be raised to the dignity of a clinical and pathological entity associated with prematurity. It is important to realize that even if one rejects

the presence of hyaline-like membrane in the lungs of premature infants as a primary cause of death, it certainly may be a predisposing factor to such conditions as pneumonia, interstitial emphysema, and pneumothorax.[20]

Summary and Conclusions

1. Of 703 hospital autopsies involving 439 neonatal deaths and 264 stillborn infants, no hyaline-like membranes were demonstrable in stillborns.

2. The etiology of this membrane in deaths of premature infants probably is not related to the aspiration of amniotic sac contents.

3. Prematurity was the only apparent predisposing factor to hyaline-like membrane formation in the lungs of these infants who die in the neonatal period.

4. When the following triad exists: (a) a clinical history of an uncomplicated, premature birth; (b) progressive respiratory embarrassment with death in one to five days; and (c) the presence of hyaline-like membrane in the lungs as the only significant autopsy finding, the case is deserving of both clinical and pathological recognition as Hyaline-like Membrane Disease.

5. Intrauterine epithelial and capillary injury from anoxia and extrauterine high concentration oxygen therapy (over 60 per cent) may be factors involved in the formation of hyaline-like membrane in premature infants.

6. Further clinical and laboratory studies are necessary to determine the effects of oxygen concentration, barometric pressure, and humidity on extracellular and intracellular respiration of premature infants.

Our thanks are due to Mr. Glen R. Mills and his staff (Department of Photography) for preparing the photomicrographs and lantern slides used in this study; Dr. Hodson Hansen for his assistance in the clinical research; and Dr. E. Stewart Taylor for his helpful suggestions.

References

1. Johnson, W. C.: Proc. New York Path. Soc. 23: 138, 1923.
2. Hood, H., and Katz, K.: Arch. Path. Anat. 267: 571, 1928.
3. Farber, S., and Sweet, L. K.: Am. J. Dis. Child. 42: 1372, 1931.
4. Johnson, W. C., and Meyer, J. R.: Am. J. Obst. & Gynec. 9: 151, 1925.
5. Farber, S., and Wilson, J. L.: Arch. Path. 14: 450, 1932.
6. Rutledge, E. K.: Unpublished Thesis, Dept. Path., University Colorado School of Medicine, 1933.
7. Rosenthal, M.: J. Pediat. 6: 71, 1935.
8. Helwig, F. C.: Am. J. Obst. & Gynec. 26: 849, 1933.
9. Steinharter, R. H.: Beitr. z. path. Anat. u. z. allg. Path. 99: 148, 1937.
10. Macgregor, A. R.: Arch. Dis. Childhood 14: 323, 1939.
11. Benner, M. C.: Arch. Path. 29: 455, 1940.
12. Ahlstrom, C. G.: Deutsche Zschr. f. d. ges. gerichtl. Med. 36: 62, 1942.
13. Potter, E. L.: Am. J. Clin. Path. 17: 524, 1947.
14. Baar, H. S.: Brit. M. Bull. 4: 178, 1946.
15. Russ, J. D.: New Orleans M. & S. J. 98: 415, 1946.
16. Schenken, J. R.: Nebraska M. J. 32: 362, 1947.
17. Arey, J. B.: New Orleans M. & S. J. 100: 258, 1947.
18. LaBate, J. S.: Am. J. Obst. & Gynec. 54: 188, 1947.
19. MacMahon, H. E.: Am. J. Path. 24: 919, 1948.
20. Ahvenainen, E. L.: Ann. med. int. Fenniae 36: 367, 1947.
21. Dick, F., Jr., and Pund, E. R.: Arch. Path. 47: 307, 1949.
22. Miller, H. C., and Hamilton, T. R.: Pediatrics 3: 735, 1949.
23. Miller, H. C., Hamilton, T. R., Wise, G. W., and Wenner, H. A.: Am. J. Path. 25: 253, 1949.

24. Harrison, H. E., Bunting, H., Ordwar, N. K., and Albrink, W. S.: J. Indust. Hyg. & Toxicol. **29**: 302, 1947.
25. Mallory, T. B., and Brickley, W. J.: Ann. Surg. **117**: 865, 1943.
26. Warren, S., and Gates, O.: Arch. Path. **30**: 440, 1940.
27. Epstein, E. Z., and Greenspan, E. B.: Arch. Int. Med. **68**: 1074, 1941.
28. Masson, P., Riopelle, J. L., and Martin, P.: Ann. d'anat. path. **14**: 359, 1937.
29. Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **73**: 465, 1943.
30. Winternitz, M. C., Smith, C. H., and McNamara, F. P.: J. Exper. Med. **32**: 199, 1920.
31. Winternitz, M. C.: Pathology of War Gas Poisoning, New Haven, Conn., 1920, Yale University Press.
32. Wolbach, S. B.: Bull. Johns Hopkins Hosp. **30**: 104, 1919.
33. Brannan, D., and Goodpasture, E. W.: Arch. Int. Med. **34**: 739, 1924.
34. Winternitz, M. C., Wason, I. M., and McNamara, F. P.: Pathology of Influenza, New Haven, Conn., 1920, Yale University Press.
35a LeCount, E. R.: J.A.M.A. **72**: 650, 1919.
35b LeCount, E. R.: J.A.M.A. **72**: 1519, 1919.
36. Potter, E. L., and Adair, F. L.: Fetal and Neonatal Deaths, ed. 2, Chicago, 1949, University of Chicago Press, p. 110.
37. Holt, L. E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, 1940, D. Appleton-Century Company, Inc., p. 97.
38. Nelson, W. E.: Mitchell-Nelson Textbook of Pediatrics, ed. 5, Philadelphia, 1950, W. B. Saunders Company, p. 343.
39. Kuhn, H. A., and Pichotka, J.: Arch. f. exper. Path. u. Pharmakol. **205**: 667, 1948.
40. Pichotka, J., and Kuhn, H. A.: Arch. f. exper. Path. u. Pharmakol. **204**: 336, 1947.
41. Karsner, H. T.: J. Exper. Med. **23**: 149, 1916.
42. Kuhn, H. A., and Pichotka, J.: Arch. f. exper. Path. u. Pharmakol. **205**: 659, 1948.
43. Miller, H. C., and Jennison, M. H.: Pediatrics **5**: 7, 1950.
44. Mossberger, J. I.: Am. J. Dis. Child. **78**: 28, 1949.
45. Reynolds, S. R. M.: Fertility and Sterility **1**: 306, 1950.
46. Herrn Geh. Medicinalrat Dr. Johannes Orth Zur Feier Seines 25 Jahrigen Proffessoren-Jubilaums Gewidmet, as published by Ahvenainen,[20] Berlin, 1903, p. 421.
47. Tesseraux, H.: Frankfurt. Ztschr. f. Path. **59-60**: 188, 1947-1949.

Discussion

DR. CARL P. HUBER, Indianapolis, Ind.—The presence of a hyaline-like membrane in the lungs of infants dying neonatally has been described with increasing frequency in autopsy studies. It appears to be a very definite entity associated with the clinical picture of secondary atelectasis and increasing respiratory embarrassment. The fact that this condition is encountered more frequently in premature infants has led Miller and his group to suggest that it actually may be an etiological factor in the occurrence of premature birth as well as responsible for the neonatal death of approaching 50 per cent of those prematures who die.

If we accept the hypothesis of the authors concerning the etiology of the hyaline-like membrane, then this added significance is eliminated. Furthermore, this recently emphasized cause of neonatal death becomes an essentially preventable factor by simply making sure that the infant does not receive too much oxygen. This paradoxical cause of anoxia can so easily be eliminated that the neonatal mortality rates in premature infants should be promptly halved.

It is unfortunate that the authors have not had sufficient time to prove their assumptions and to produce cluinical evidence of their importance. Examination of their experimental data is extremely intriguing but there is certainly insufficient evidence to justify their complete acceptance. I do not wish to detract from their work by saying this, but rather to congratulate them upon the start of a pioneer study.

The assumption that a damaging effect is produced directly upon the pulmonary epithelium by high tensions of oxygen is perhaps the simplest explanation for the development of a hyaline membrane, but it is only one of several possible explanations. Information concerning the degree of oxygen saturation of the blood in such infants, or in the animals studied experimentally, might well support the thesis that the effect is primarily a central nervous system one with direct damage to the respiratory center. Reflex spasm of the bronchioles might so alter intrapulmonary pressures that fluid from the tissues is poured into the air passages to produce the hyaline-like membrane. It is stimulating to consider the possibilities for additional investigation that this report has indicated.

DR. BRUNS (Closing).—The work of Pichotka and Kuhn has been especially interesting to us, in that they were able to produce this membrane with such a degree of ease. Also, in their experiments, no clinical or pathological pulmonary changes occurred in the animals subjected to high oxygen concentrations at reduced atmospheric pressures. Since the neonatal incidence of the hyaline-like membrane in Kansas City is 50 per cent, and in Denver, 25 per cent, perhaps the reduced atmospheric pressure may account for the different incidence.

The oxygen concentrations at normal or increased pressures, which are detrimental to alveolar epithelium, are probably something over 40 to 60 per cent. The oxygen concentrations in the various types of incubators, hoods, and cones have been recorded as ranging from 30 to 95 per cent.

The observation has been made that the incidence of diseases like pulmonary hyaline-like membrane, retrolental fibroplasia, and sclerema has increased with the modernization of nurseries. With the acquisition of piped-in oxygen, an abundant supply of incubators, and the general philosophy that "if a little bit of oxygen is good, a whole lot ought to be better," perhaps higher concentrations of oxygen are being delivered to premature infants with resultant harmful effects. At least, further research in this field certainly seems indicated.

CARCINOMA OF THE CORPUS UTERI IN YOUNG WOMEN*

MALCOLM B. DOCKERTY, M.D., SIM B. LOVELADY, M.D.,** AND
GLENN T. FOUST, JR., M.D., ROCHESTER, MINN.

(From the Divisions of Surgical Pathology and of Medicine, Mayo Clinic and the Mayo Foundation)

IT IS conceded that whereas carcinoma of the uterine cervix affects women less than 40 years of age in perhaps 25 per cent of any sizable group of cases, the uterine corpus enjoys on an average an additional decade of relative immunity from malignant processes.[2, 17] Most of the larger series of carcinomas of the uterine corpus include occasional exceptions to this general rule[1, 6, 9, 11, 12, 22] and the figure of 5 per cent has been accepted as the incidence of its occurrence prior to that delightful period when "life begins." This was the actual incidence found by Speert,[21] who, in 1949, devoted an article to the subject of carcinoma of the uterine corpus in young women. Five of his 14 patients were 35 years of age or younger, and 9 were in the 35-year to 40-year bracket. Further interest in the "age factor" of the problem was created by Sommers, Hertig, and Bengloff[20] in their 1949 report on 8 personal cases and 8 referred from other sources. The ages of their patients ranged from 19 to 35 years and they found a total of 30 additional examples in the literature including those of Speert,[21] Jones and Brewer,[8] Hirst,[6] Smith,[19] and others.[11, 12]

Our particular interest in this subject was stimulated by observing several young women with uterine carcinoma who presented histories of amenorrhea and sterility, and also exhibited marked obesity, hirsutism, and hypertension. Their lesions of the uterine corpus were unusual in that they featured a mixture of glandular cancer and squamous-cell epithelioma and their ovaries were relatively large and cystic with thick cortical rinds. We found that others had reported similar findings[16, 20] and had attempted to link them to an excess of estrogenic stimulation.

Review of our surgical pathologic files revealed a substantial group in which the diagnosis of endometrial carcinoma had been made on young women and our decision to report them in this series was predicated on the hope that some new facts might be added to the literature on this subject.

Materials and Methods

After a careful screening process designed to delete cases with doubtful diagnoses and those in which no pathologic tissue was available for study, there remained for analysis 36 examples of bona fide carcinoma of the uterine corpus affecting women less than 40 years of age. The material, all of which was surgical, was gathered from the files of the Mayo Clinic from 1905 through

*Read at the Eighteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Milwaukee, Wis., Sept. 21 to 23, 1950.

**Present address, Houston, Texas.

1944. Records on these cases were secured and scrutinized for data pertaining to family history, marital status, fertility, parity, age at onset of menarche, menstrual history, previous operation, and the story of the presenting illness. For physical findings, special emphasis was placed on the weight, height of the patient, presence or absence of obesity and hirsutism. All blood pressure levels were recorded. Any notes made regarding positive findings on pelvic examination were carefully tabulated. Operative results were studied for gross description of pelvic organs which were not removed. Factual data relating to other forms of therapy including preoperative and postoperative treatment with roentgen rays and radium were recorded and correlated with follow-up studies to determine prognosis.

From the pathologic standpoint all of the removed organs and the curetted tissue had been carefully preserved and were available for study. Meticulous notes were made on the size and character of the carcinoma, the presence or absence of uterine polyps, and the appearance of uninvolved endometrium. The myometrium was sectioned for an estimation of the degree of gross penetration and for the presence of associated myomas and adenomyomas. Cervical erosions were carefully looked for. Particular attention was paid to the ovaries, since others have reported fibrocystic disease and hyperthecosis as affecting the ovaries of women with carcinoma of the uterine corpus.[20, 26] The presence of old and recent corpora lutea was recorded for reasons which will be developed later. Finally, multiple representative sections were taken from the various lesions noted in each case and these were blocked and cut, using both the paraffin and the freezing techniques. Hematoxylin and eosin stain was routinely employed.

Clinical Findings

Incidence.—Over the 40-year period encompassed by the study, 1,694 clinic patients were treated for carcinoma of the uterine corpus. Our 36 cases comprised 2.1 per cent of this total, a figure which is considerably lower than the 5 per cent incidence cited by Speert.[21]

Age.—Fifteen of the patients were less than 35 years of age but all except 4 of these had passed their thirtieth birthdays. The remaining 21 patients were in the 35-year to 39-year age bracket, and 7 of this group were exactly 39 years old. This shift of increasing incidence toward the older age segments of the spectrum analyzed is in keeping with the findings of others.[2]

Marriage and Pregnancy.—Eight of the group were single and 28 were married. Seventeen of the 28 had been pregnant one or more times but only 11 of the entire group had borne viable offspring. Only 7 had had more than one pregnancy and only 4 had had more than one child. (The total number of children born to the entire group was 20.) Most of the recorded deliveries had occurred from ten to fifteen years prior to the time of admission, the two shortest known intervals being five years and nine years, respectively. This analysis denotes a striking incidence of infertility, again similar to the recorded observations of others.[5-16, 20, 22]

Onset and Character of Menses.—The average age at onset of menses was 13.1 years, and in 2 instances only could the menarche be described as being delayed. In 30 patients, menses had begun regularly and had remained so for a number of months or years, a fair number having had no menstrual difficulty until after marriage. Five had experienced an abnormal menarche, and in 1 case vicarious menstruation was described as having occurred. With these beginnings, practically all of the patients related stories of variable but usually severe menstrual difficulties as summarized in Table I. Nineteen patients had suffered from menometrorrhagia for periods varying from one month to twenty

years, and in seven the duration was in excess of five years (Table I). Ten had suffered primarily from menorrhagia and 4 from metrorrhagia for comparable periods of time. Polymenorrhea was noted in 2; 5 had suffered from the effects of dysmenorrhea. In the group with excess bleeding there were 10 women in whom amenorrhea of long or short duration had been a noteworthy symptom. Five of these 10 exhibited additional features of the Stein-Leventhal syndrome. Leucorrhea had been a major source of difficulty in 10. Thirteen patients had undergone one or more prior curettages in unsuccessful attempts to control their excess bleeding, and in 2 instances radium had been subsequently placed in the uterine cavity with like purpose. Transfusions had been necessary in 2 cases.

TABLE I. ANALYSIS OF MENSTRUAL HISTORIES

TYPE OF HISTORY	CASES	DURATION MORE THAN 5 YEARS
Menorrhagia	10	6
Metrorrhagia	4	1
Menometrorrhagia	19	7
Polymenorrhea	2	2
Normal menses	1	
Amenorrhea	10	

Major Symptoms.—For the most part the presenting symptoms comprised the menstrual abnormalities cited in the foregoing. However, 10 patients complained of sterility or infertility, and 2 patients had undergone extensive investigation along these lines. Four had come because of a recent diagnosis of "cancer." Abdominal tumor, backache, headache, arthritis, weakness, loss of weight, and constipation competed for places in the list of incidental symptoms.

Physical Examination

In 32 instances clinical notes had been made concerning the general appearance of the patient, and of this group 13 were described as being obese with weights in excess of 150 pounds. Weights exceeding 200 pounds were recorded for 6 patients. Heights were not always listed but the 5-foot, 4-inch average for the group supported the notion that many of the patients were truly overweight. Hertig and others[20, 21] have also remarked on this finding. Three of the obese subjects also exhibited hirsutism. Blood pressures were recorded on 26 patients, and in 10 the readings were in the hypertensive range. Seven of these 10 patients were also obese, 2 had clinical diabetes, and 1 was hirsute.

Contrary to what might be expected from the histories of bleeding, less than 20 per cent of the patients exhibited weakness and pallor. Mammary nodules in 2 patients were thought to be fibroadenomas, and one patient was listed as having bilateral mastitis. Except for the results of pelvic examination, the other findings were more or less incidental. Brief references will be made to them in our descriptions of "associated pathologic lesions."

Pelvic Examination.—The vulva and the vagina each contributed but one positive finding; namely, hypertrophy of the labia minora in 1 case and a vaginal nodule of recurrent carcinoma in another. Cervical abnormalities were numerous with "bloody discharge from the external os" being recorded in nine cases. The cervix was enlarged or otherwise deformed in 5 instances and more or less fixed in 4. Four patients exhibited cervical erosions, 3 had moderately to markedly cystic cervices, and in two patients polyps were visualized. On bimanual examination the uterus was described as being enlarged in 22 cases, and retroflexed in four of these. Adnexal masses were felt in 8 instances, and in four cases there appeared to be fixation of pelvic structures. No positive pelvic abnormalities were noted in three patients.

Laboratory Findings

Of the various laboratory tests performed, the hemoglobin determination alone gave results which were significant, but in a negative sort of way. With excessive and prolonged uterine bleeding one might have expected a high incidence of severe secondary anemia. Yet only eight of the patients had hemoglobin readings of less than 10 Gm. per 100 c.c. of blood, and of these only 3 had obvious clinical manifestations of loss of blood. Moreover, 2 of the remaining 5 with low hemoglobin readings had not been suffering from menometrorrhagia. A short history of excessive uterine bleeding seemed to be more significant than did a long one in the production of low blood levels of hemoglobin.

Nothing of a positive nature was revealed by the routine roentgenographic studies carried out on our group of patients. Stein and Leventhal[25] have emphasized the value of pneumoroentgenography in the matter of visualizing the ovaries of patients with the syndrome which now bears their name.

Treatment

Total abdominal hysterectomy was performed on 24 patients, the operation being immediately preceded by curettage in all instances except those in which either a previous diagnosis of carcinoma had been made microscopically or in which the operation was performed for "fibroids," the carcinoma being found incidentally. Hysterectomy with unilateral salpingo-oophorectomy was done on 4 patients whose contralateral tubes and ovaries had been removed previously. Hysterectomy alone was the operation performed on 3 patients seen in the earlier years of study. One patient whose uterus had been removed elsewhere underwent laparotomy at the clinic with biopsy of an irremovable recurrent pelvic carcinoma. In still another the operation consisted in biopsy of a recurrent vaginal nodule. In 3 very obese patients curettage alone was performed, the patients being then referred to the Section on Roentgen and Radium Therapy, for further treatment. In addition to these 3 patients, 8 received postoperative roentgen or radium therapy or both. In several instances radium therapy had been employed several years before the diagnosis of carcinoma had been made. There was no good evidence to indicate that the radium in these cases had induced the development of carcinoma.[23] It seemed more logical to assume that therapeutic "irradiation" in doses calculated to control functional uterine bleeding had failed to halt the subsequent development of endometrial carcinoma.

"Follow-up" letters were sent to each of the 36 patients but the response was disappointing in that in 23 cases only was useful information made available. Of these, 18 patients were living five years or longer postoperatively, 4 had died from the effects of their carcinoma of the uterine corpus (3 certainly and 1 presumably), 1 was alive but with an inoperable recurrence. Thirteen of the letters were not answered. It remains possible that several of this group of 13 have succumbed from the effects of their malignant processes.

Gross Pathologic Findings

Thirty-three formalin-preserved uteri were available for study. Their average weight was 156 grams, and only 5 specimens weighed less than 100 grams, which is generally accepted as being normal. In only 8 of the 28 "heavier" specimens did the presence of fibromyomas contribute material bulk, the remaining 20 exhibiting degrees of myohypertrophy. This finding becomes more noteworthy when we recall that the majority of these uteri had never fulfilled any reproductive function.

Grossly (Fig. 1, *a*) it was difficult to catalogue the type of endometrial lesion owing to the trauma of previous curettage, but Table II represents an attempt at subdivision.

Major degrees of myometrial invasion were noted in 3 specimens, and an additional 8 exhibited some evidence of penetration. Two cases of diffuse polypoid carcinoma demonstrated involvement of the endocervix.

Fig. 1, *a*.—Diffuse polypoid carcinoma of the corpus uteri in a young woman with clinical Stein-Leventhal syndrome.

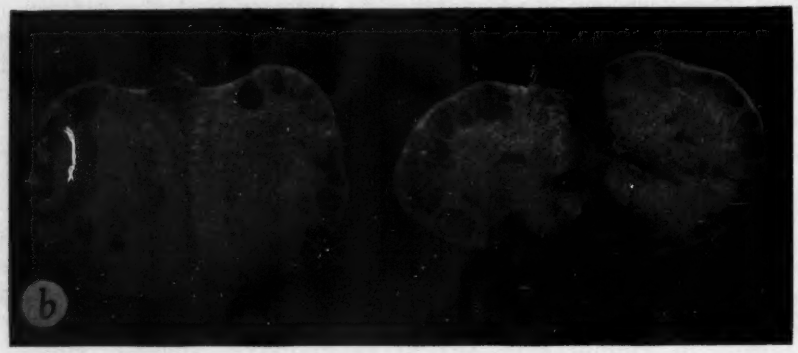


Fig. 1, *b*.—The ovaries from the same case as in Fig. 1, *a*, showing solid centers and thick cortical rinds with an intervening zone of tissue occupied by numerous simple cysts.

Associated lesions of the corpus observed in the 33 uteri consisted of fibromyomas in 15 (myosarcoma in 1), adenomyoma in 1, endometriosis in 3 and subperitoneal inclusion cysts in an unrecorded number. A few postoperative and a few inflammatory adhesions were noted in passing. Cervical abnormalities consisted of those listed in the clinical findings plus the 2 instances of involvement of the endocervix by direct extension from the endometrial growth.

Gross tubal lesions were not remarkable and they consisted of the usual run of cysts of Morgagni and 1 tuboovarian abscess.

One or both ovaries were present in 28 preserved specimens, in 2 cases they had been lost and in the remaining 6 cases they had not been removed. In 14 cases (50 per cent) the ovaries were large and quite cystic. Measurements up to 5 cm. in diameter were not unusual and their weights varied from 15 to 60 grams per ovary (normal perhaps 8 to 10 grams). In 6 cases they were invested with thick cortical rinds under which lay a ring of large and small unruptured follicular cysts (Fig. 1, *b*). In these specimens no old or recent corpora lutea were in evidence and the picture was typical of the appearance of the ovaries in the Stein-Leventhal syndrome.[24, 25] In the entire group of large cystic ovaries the enlargement was usually symmetrical and bilateral.

Seven specimens revealed ovaries which were cystic but normal in size; 3 "pairs" were sclerotic but otherwise normal; in 2 cases the ovaries were solid but not sclerotic. One ovary was the seat of a cystadenocarcinoma, and another formed part of a tuboovarian abscess. Recent corpora lutea were observed in 6 ovarian specimens and old corpora lutea in an equal number.

TABLE II. GROSS CLASSIFICATION OF LESIONS

	CASES
Polypoid carcinoma	
Diffuse	7
Circumscribed	7
Malignant adenoma	7
Ulcerative or infiltrative or both	5
Unclassifiable*	10

*Including the 3 cases in which curetted material alone was available.

Microscopic Examination

Twenty-six of the endometrial growths were adenocarcinomas, and 10 were adenoacanthomas. This is a higher proportion of the latter than we have found in the literature, and it cannot be explained entirely on the basis of our having made multiple sections through the growths. The adenocarcinomas ran the entire gamut of Broders' grading but the adenoacanthomas were all grade 1 lesions with one exception (Figs. 2, *a* through 3, *a*). Table III is an analysis based on grading the neoplasms.

In the matter of extension, 3 specimens exhibited deep penetration of the myometrium, and 2 exhibited involvement of the cervix. In addition, 2 patients who had been treated elsewhere demonstrated in their respective pelvic recurrences invasion of the vagina and extensive pelvic metastasis. Minor degrees of myometrial spread were observed in 10 additional specimens.

TABLE III. MICROSCOPIC FEATURES: TYPE AND GRADING (BRODERS' METHOD)

	GRADE			
TYPE OF CARCINOMA	1	2	3	4
Adenocarcinoma*	13	8	4	1
Adenoacanthoma	9	1	0	0

*One of the adenocarcinomas was associated with an underlying grade 1 leiomyosarcoma, apparently beginning in a fibromyoma.

Examination of uninvolved portions of the endometrium was often impossible because the carcinoma was diffuse or the curettage "complete." In 14 instances the picture was that of hyperplasia (Table IV), and in 7 of these islands of carcinoma cells lay intermingled with or alongside of benign endometrial glands. However, in 7 instances the uninvolved endometrium exhibited coiling

of glands and other features of secretory change. In 4 of these the picture was definitely that of premenstrual endometrium (Fig. 3, *b*). Jones and Brewer[8] also observed this type of endometrium in patients with carcinoma of the uterine corpus. Herrell[5] noted the rarity of differentiative endometrium in association with carcinoma of the corpus but his cases probably included few or none from

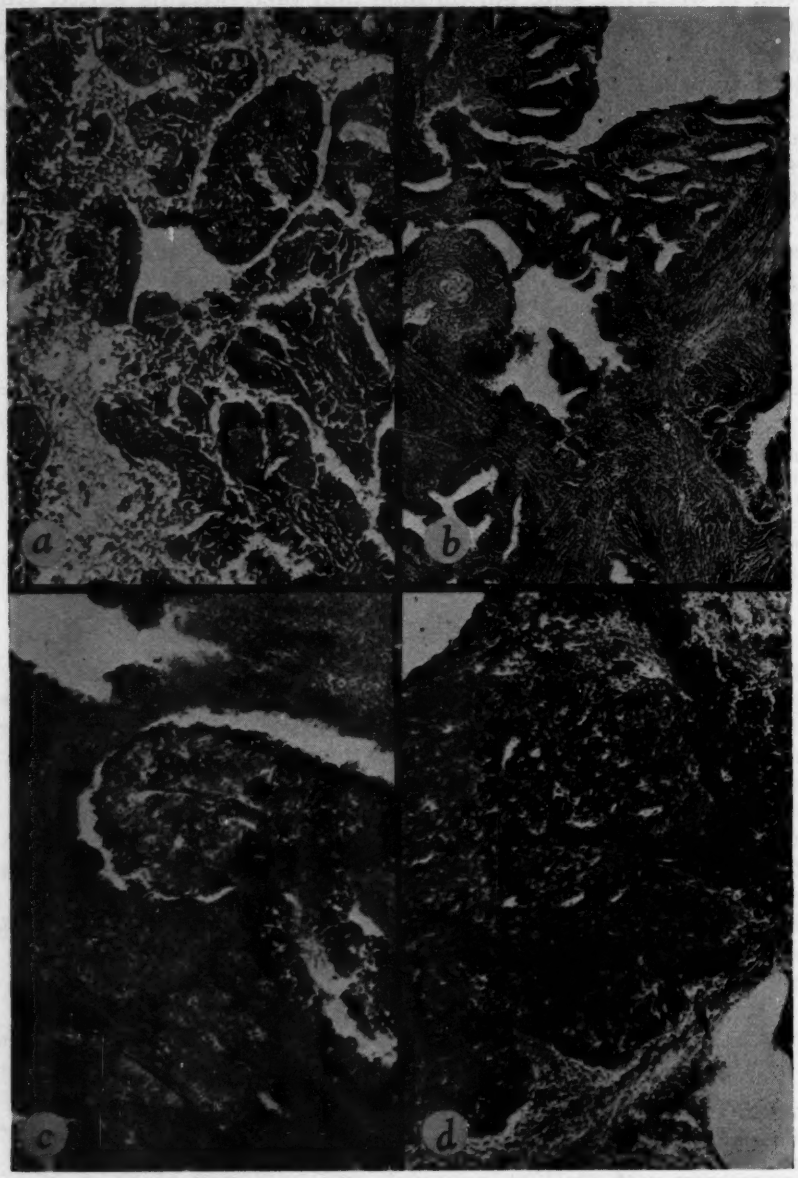


Fig. 2.—*a*, Grade 1 papillary adenocarcinoma. The growth exhibits good cellular differentiation (hematoxylin and eosin, ×85).

b, Grade 2 adenoacanthoma showing irregularity of gland formation. Malignant metaplasia with pearly body formation is shown in upper central portion. The section was taken from an area of myometrial invasion (hematoxylin and eosin, ×45).

c, Grade 3 adenocarcinoma plugging a lymphatic space in the myometrium. Reproduction of glandlike structures is poor and it reflects dedifferentiation of cellular elements (hematoxylin and eosin, ×60).

d, Grade 4 adenocarcinoma of corpus uteri. The carcinoma cells are growing in solid sheets and they exhibit very little tendency to reproduce glandular spaces (hematoxylin and eosin, ×60).

Fig. 3.—*a*, Grade 1 adenoacanthoma of the corpus uteri showing a pattern of irregularly branched glands and nests of malignant squamous cells (hematoxylin and eosin, ×55).

b, An uninvolved portion of endometrium from the same case. The picture is that of the late differentiative phase of the menstrual cycle (hematoxylin and eosin, ×60).

c, Portion of a well-formed corpus luteum from same case (hematoxylin and eosin, ×45).

this series. It is our feeling that analysis of any sizable group of carcinomas of the corpus in young women will bring forth some examples of "secretory endometrium" and of normal-appearing corpora lutea in the ovaries (Fig. 3, *c*). However, the occurrence of endometrial carcinoma is extremely rare when, as in surgical castration, all the ovarian hormonal influence is withdrawn.

Metaplasia involving the glands of the endocervix was noted in 5 (15 per cent) of 33 uteri (Fig. 4). Speert[21] found a somewhat higher incidence of this change and felt that, as with hyperplasia of the endometrium, it indicated prolonged estrogenic stimulation. Gardner and co-workers[3] have induced metaplasia and even carcinomatous changes in the cervices of mice, using estrogens.

Fig. 4.—Section of a cervix showing metaplasia in one of our cases of carcinoma of the corpus uteri in young women (hematoxylin and eosin, ×100).

Other interesting lesions involving the Fallopian tubes, the vagina, the vulva, and the breast are noted in Table V along with a miscellany of conditions which were not strictly gynecologic. It will be noted with interest that in 6 of these 36 cases carcinomas developed, synchronously or metachronously, in other parts of the body.

TABLE IV. TYPE OF ENDOMETRIUM SURROUNDING THE CARCINOMA

ENDOMETRIUM	CASES
Proliferative (so-called hyperplasia)	14
Early differentiative	4
Late differentiative	3
Unavailable (curettage only, diffuse carcinoma, and so forth)	15
Total	36

Much of the ovarian "pathology" has been covered in our gross descriptions but certain microscopic features were noteworthy. Most of the group with cystic ovaries exhibited thick cortical rinds which would seem to constitute a barrier to normal ovulation. This fibrous rind reached its maximal thickness in 6 cases presenting features of the Stein-Leventhal syndrome. In none of these were old or recent corpora lutea observed. All 12 ovaries available from patients with this syndrome contained numerous primordial follicles.

The ovaries which were studied from the remaining 22 patients contained identifiable corpora lutea in 9 cases only, and in but 6 of these could the structures be termed recent (Fig. 3, *c*). The presence of fresh corpora correlated in 3 instances the finding of secretory endometrium. Stromal-cell hyperplasia with or without luteinization in the absence of identifiable corpora lutea was observed in 5 specimens (Fig. 5, *a* and *b*), a finding which others have noted in cases of

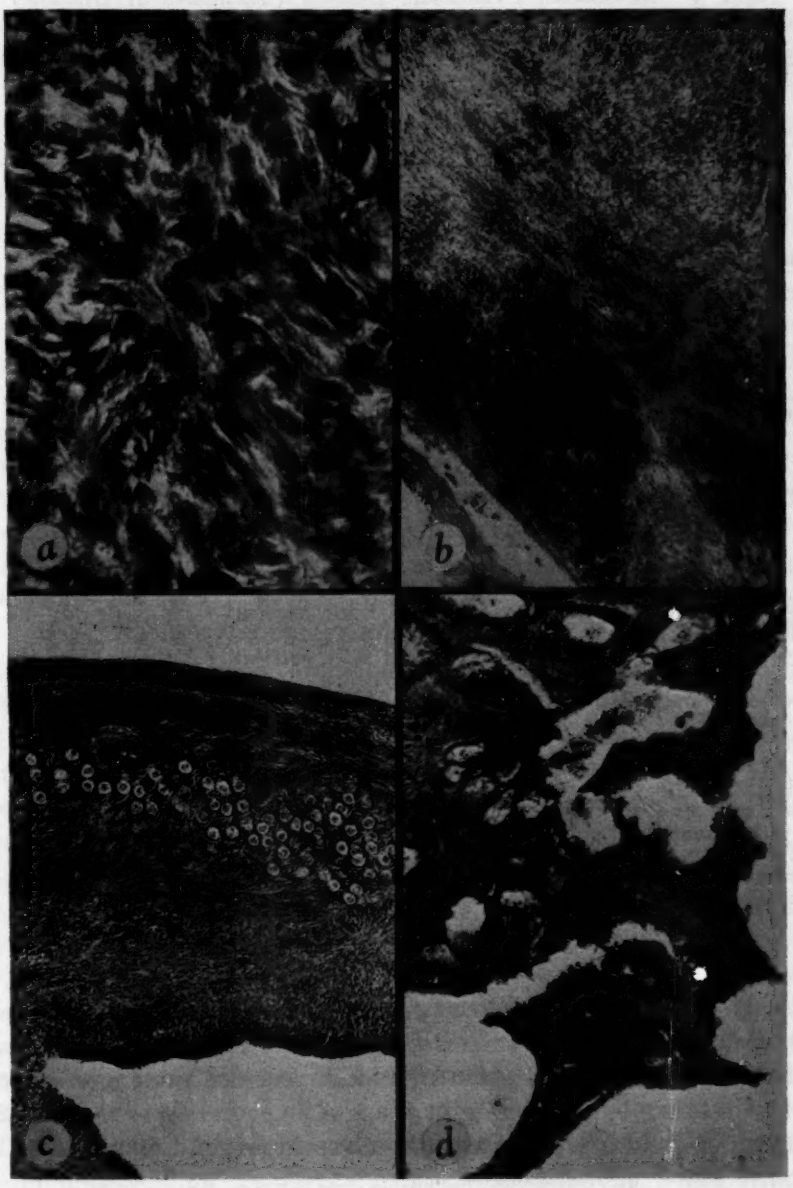


Fig. 5.—*a*, Section of an ovary from one of our cases showing hyperplasia of stromal cells which are large with plump spindle-shaped nuclei (hematoxylin and eosin, ×400).

b, So-called luteinization of stromal cells is apparent in this case. The dark-staining areas in the reproduction are "positive" for the presence of lipoids (Sudan III, ×100).

c, Ovary from a case with Stein-Leventhal syndrome and carcinoma of the corpus uteri. Under a thick fibrous rind appear large numerous primordial follicles, each one containing an ovum. Portion of a simple cyst is also shown at lower right (hematoxylin and eosin, ×40).

d, Primary and independent grade 1 mucous cystadenoma of the right ovary in a young woman who also had carcinoma of the corpus uteri (hematoxylin and eosin, ×60).

carcinoma of the uterine corpus.[26] Fifteen cases in addition to the 6 mentioned previously exhibited variable numbers of primordial follicles in the ovarian cortices (Fig. 5, *c*). Our 1 example of ovarian cystadenocarcinoma we regarded as being independent of any relation to the uterine lesion (Fig. 5, *d*). The same might be said of our single association of tubovarian abscess (Table VI).

TABLE V. ASSOCIATED PATHOLOGIC LESIONS (EXCLUSIVE OF OVARIAN)

SITE	LESION	CASES
Myometrium	Sarcoma in fibromyoma	1
	Fibromyoma	15
	Adenomyoma	1
	Endometriosis	3
Cervix	Polyp	2
	Erosion	2
	Metaplasia	5
	Invasion by carcinoma	2
Fallopian tube	Tubovarian abscess	1
	Cysts of Morgagni	3
Vagina	Recurrent carcinoma	1
Breast	Lipoma	1
	Fibroadenoma	2
	Cystic mastitis	1
Miscellaneous	Carcinoma of face	1
	Carcinoma of rectum (independent)	3
	Polyp of rectum	1

TABLE VI. OVARIAN CHANGES NOTED IN 28 SPECIMENS

CONDITION	CASES
Large, cystic ovaries (15 to 60 grams) with thick cortical rinds	6
Large, cystic ovaries (15 to 60 grams) without thick cortical rinds	8
	14
Cystic but of average size	7
Solid and sclerotic	3
Solid but not sclerotic	2
Primary ovarian cystadenocarcinoma	1
Tubovarian abscess	1
Parovarian cyst	1
Absence of corpora lutea	19
Primordial follicles	21
Luteinization of stromal cells	5
Endometriosis	3

Comment

Much of the material pertinent to a discussion has been touched on in foregoing paragraphs. However, certain points are deserving of emphasis.

In the entire group of 36 women the occurrence of prolonged menometrorrhagia, often interrupted by months or years of amenorrhea, is brought into even sharper focus by the failure of these symptoms to respond to the usual methods of treatment based on hormone therapy, curettage, implantation of radium, and so forth. The incidence of infertility in the 28 married patients (0.7 child per couple) was difficult to explain except on the basis of some hormonal disturbance, and the designation "ovarian dysfunction" was used in describing a number of the patients who were obese and who also were "hypertensive." No less than 7, or almost 20 per cent, of the patients presented four or more of the cardinal features seen in the Stein-Leventhal syndrome.[7, 20, 24, 25] Four of these

patients weighed more than 200 pounds and 2 were quite hirsute. Five of 6 uteri available from these patients were large. Uninvolved portions of endometrium were found in 4 of the 7 cases and all exhibited hyperplasia. We have recently observed 3 additional patients more than 40 years of age, who exhibited this complex and in whom carcinoma of the endometrium developed. We feel very strongly that more attention should be paid to this complication of the Stein-Leventhal syndrome. Evidence such as we have herein presented has been interpreted as indicating that these patients were suffering from conditions of chronic hyperestrinism which eventually proved carcinogenic.[4, 10, 13-16, 20, 21] Attractive as this hypothesis may be, we cannot make in behalf of it any strong supporting claims. As with others, our evidence has been indirect and no studies were conducted on this group of patients relative to their excretion of estrogen.

The finding of old or recent corpora lutea in the ovaries of 9 patients does not refute the "estrogenic" notion. It merely signifies that ovulation occasionally occurs in these women. Indeed, of more significance was the absence of corpora lutea from the ovaries of such a high percentage of young women.

Finally, the discovery of secretory endometrium in 7 patients with localized growths of the uterine corpus has in our opinion about the same significance as the foregoing. Even in the endometrial hyperplasia induced by granulosa-cell tumors of the ovary, luteinization in the latter will change the picture of the former to one of a secretory activity. Carcinoma of the endometrium can occur side by side with the microscopic picture of premenstrual endometrium and the age group herein studied is the ideal one for the demonstration of such strange histologic bedfellows.

Summary and Conclusions

1. Of 1,694 patients with carcinoma of the uterine corpus, 36 (2.1 per cent) were less than 40 years of age.

2. In this group of 36 patients, symptoms for the most part were menstrual and featured irregular menometrorrhagia, often with amenorrhea, leucorrhea, and related difficulties, all more or less intractable to ordinary therapeutic measures. Anemia was paradoxically rare. It is to be emphasized that these commonplace symptoms were oftentimes owing to malignant change in the endometrium. Early and repeated curettage along with vaginal smear studies are accordingly indicated in young patients suffering from such symptoms.

3. Clinically, obesity with sterility, a high incidence of hypertension, and occasional hirsutism and diabetes were prominent features. Seven of the 36 patients studied exhibited features of the Stein-Leventhal syndrome. The possibility of carcinoma of the uterine corpus complicating this syndrome has not received sufficient emphasis.

4. Pathologically the uterine growths were not remarkable except for an increased incidence of malignant adenoma. Microscopically, a surprisingly large number of the lesions were adenoacanthomas. A high incidence of associated fibromyoma, myohypertrophy, endometrial hyperplasia, cervical glandular metaplasia, and cystic ovarian changes possibly indicated the existence of chronic "hyperestrogenism." We have no direct evidence that such a condition existed. In at least 6 specimens proof of recent ovulation was afforded by a study of the endometrium and of the ovaries.

5. Treatment should consist of total abdominal hysterectomy followed by postoperative therapy with radium or roentgen rays or both. The employment of small doses of radium as a means to control bleeding is to be decried until the presence of carcinoma has been ruled out by diagnostic curettage. Our evidence, however, did not support the view that radium so employed had actually induced the development of carcinoma.[18]

References

1. Danforth, W. C.: Textbook of Surgery, ed. 5, Philadelphia, 1949, W. B. Saunders Company, p. 1361.
2. Diddle, A. W.: Am. J. Obst. & Gynec. 59: 1373, 1950.
3. Gardner, W. U., Allen, Edgar, Smith, G. M., and Strong, L. C.: J. A. M. A. 110: 1182, 1938.
4. Gusberg, S. B.: Am. J. Obst. & Gynec. 54: 905, 1947.
5. Herrell, W. E.: Am. J. Obst. & Gynec. 37: 559, 1939.
6. Hirst, B. C.: Am. J. Obst. & Gynec. 18: 104, 1929.
7. Ingersoll, F. M., and McDermott, W. V.: Am. J. Obst. & Gynec. 60: 117, 1950.
8. Jones, H. O., and Brewer, J. I.: Am. J. Obst. & Gynec. 42: 207, 1941.
9. Lockhart, H. A.: Am. J. Obst. & Gynec. 30: 76, 1935.
10. Loeb, Leo: J. M. Research 40: 477, 1919.
11. Mazzola, V. P.: Am. J. Obst. & Gynec. 36: 698, 1938.
12. Morehead, R. P.: Arch Path. 38: 141, 1944.
13. Novak, Emil: Unpublished data.
14. Novak, Emil, and Rutledge, Felix: Am. J. Obst. & Gynec. 55: 46, 1948.
15. Novak, Emil, and Yui, Enmei: Am. J. Obst. & Gynec. 32: 674, 1936.
16. Randall, C. R.: J. A. M. A. 127: 20, 1945.
17. Scheffey, L. C.: South, M. J. 42: 44, 1949.
18. Smith, F. R., and Bowden, Lemuel: Am. J. Roentgenol. 59: 796, 1948.
19. Smith, G. V. S.: New England J. Med. 241: 410, 1949.
20. Sommers, S. C., Hertig, A. T., and Bengloff, Harold: Cancer 2: 957, 1949.
21. Speert, Harold: Cancer 1: 584, 1948.
22. Speert, Harold: Surg., Gynec. & Obst. 88: 332, 1949.
23. Speert, Harold. and Peightal, T. C.: Am. J. Obst. & Gynec. 57: 261, 1949.
24. Stein, I. F.: Am. J. Obst. & Gynec. 50: 385, 1945.
25. Stein, I. F., and Leventhal, M. L.: Am. J. Obst. & Gynec. 29: 181, 1935.
26. Woll, Ephraim, Hertig, A. T., Smith, G. V. S., and Johnson, L. C.: Am. J. Obst. & Gynec. 56: 617, 1948.

Discussion

DR. HERBERT E. SCHMITZ, M.D., Chicago, Ill.—To the substantial evidence already available, Dr. Dockerty and his associates have added further evidence that endometrial cancer is more frequent in the patient with hyperestrinism. The characteristic clinical picture of this female has been painted for us by Herrell, Randall, Jones and Brewer, Corscaden, Gusberg, Speert, and many others. To the original sketch of an obese hypertensive female of a high sterility and low fertility, the overtones of a sixth-decade individual showing all the signs of prolonged unopposed estrogen stimulation have been drawn. In 18 per cent an accompanying granulosa-theca-cell tumor is present, and the incidence of breast carcinoma is four times that of the average. Randall observes that if these signs of excess estrogenic stimulation are absent, as evidenced by atrophy of the vulvar and vaginal epithelia, it is rare to find endometrial carcinoma.

In a further attempt to describe our classic example, Dr. Dockerty has opened her to further inspection and through microscopic examination proved that what we knew the picture to be clinically is based on sound evidence; namely, hyperplasia of the endometrium in association with carcinomatous change, epidermidalization or squamous metaplasia of cervical glands and retained follicles in an ovary containing multiple cysts without evidence of recent ovulation and a thickened sclerosed outer coat.

Our incidence of this disease in patients younger than 40 years of age is 6.56 per cent, a total of 9 cases in a ten-year period. That such a discrepancy in incidence can exist is understandable when we consider that Speert found an incidence of 5 per cent in the 255 cases he studied. Here again we find definite evidence of hyperestrinism and must agree with the author and others that menstrual irregularity manifested by menometrorrhagia, amenor-

rhea, and leucorrhea present over a long period in an individual who is sterile or infertile, though she be in the second or third decade of life, must not be ignored or treated lightly. That these patients frequently show hyperplasia of the endometrium in areas not showing malignant change demonstrates clinically that prolonged unopposed estrogen stimulation may be carcinogenic. We must not, however, confuse the issue and conclude that hyperplasia of the endometrium is a precancerous lesion.

A further examination of our data again demonstrates that the greatest number of these patients suffering from endometrial carcinoma are in the sixth decade of life, and we must agree that they have a delayed menopause as well as a "bloody menopause," using the descriptive phrase of Corscaden.

Of extreme interest is our observation that during the time the 137 patients with endometrial carcinoma were admitted, 499 cases of cervical carcinoma were seen, a ratio of 1 to 3.6. We believe this indicates that the disease is more prevalent than supposed and is discovered more readily. We hasten to add, however, the distressing observation that the average patient delay was 9.76 months, while the physician delay was but 1.7 months. *Further lay education is necessary,* in spite of the plea from some of our more complacent confreres that we are producing cancer phobias at an alarming rate.

As to the treatment of endometrial carcinoma, I am at variance with the authors, and offer in defense of preoperative irradiation the account of numerous uteri, with proved adenocarcinoma, which no longer showed evidence of disease after irradiation, removal, and serial section. To strengthen my premise further, may I include the five-year survivals in our most recent 137 cases treated by our described technique, using the Y applicator of radium and x-rays of 800 kv. intensity. Six of these patients did not complete the prescribed course of therapy and, therefore, are not included in (Table I).

TABLE I. ENDOMETRIAL CARCINOMA,* 1933-1945

GROUP	RESULTS	RADIATION	SURGERY ALONE	COMBINATION		GROUP SALVAGE
				PREOP.	POSTOP.	
I	Alive 5 years	6	4	8	6	85.7
	Dead	4	0	0	0	
	% Survival	60.0	100.0	100.0	100.0	
II	Alive 5 years	8	1	8	5	70.9
	Dead	4	0	2	3	
	% Survival	66.6	100.0	80.0	62.5	
III	Alive 5 years	6	0	3	3	54.5
	Dead	6	0	1	3	
	% Survival	50.0	–	75.0	50.0	
IV	Alive 5 years	1	0	2	4	14.0
	Dead	35	1	0	7	
	% Survival	2.7	–	100.0	36.3	

*Total five-year survival, 50.0 per cent.

DR. A. F. LASH, Chicago, Ill.—The subject of endometrial carcinoma, although not as urgent as cervical carcinoma, has been brought to us by the Mayo group and has brought forth the importance of considering carcinoma in young women.

Too often we have gone along feeling that carcinoma of the endometrium would occur only in older women. It is of interest to know just how the diagnosis was made in those women who had amenorrhea. The women who have amenorrhea will be treated for sterility or infertility, and certainly the diagnosis of carcinoma will be overlooked. It occurs to me it would be of interest to all of us to know how the diagnosis is made in those specific instances.

In addition to the clinical picture, so well presented, the pathological studies of the endometrial carcinomas are of great importance because of their mode of extension. We may find that the carcinoma cells may be found in the Fallopian tubes or in the ovaries. We should like to know also about the lymph node involvement associated with endometrial carcinoma, since this site of metastases is not given enough attention.

Although Dr. Schmitz is a strong proponent of radiological therapy, the majority of men today still treat carcinoma of the endometrium surgically, with preoperative or postoperative x-ray therapy, or both.

Inasmuch as our carcinoma surgery today is being more and more extended, may we not improve our five-year salvage by removing many of these involved nodes which are so often overlooked in the endometrial carcinomas?

Due cognizance has been taken of them with cervical carcinoma, but it is unfortunate when you see a woman come back a year later, after the removal of an endometrial carcinoma, with inguinal gland involvement indicating that the lymphatics have been involved and the inguinal nodes very likely were involved also, and that if they had been removed the year before the woman's life might have been saved.

There is one other question I should like to ask the authors, and that is, whether they found these polyhedral cells in the ovaries, as described by Shaw and Dastun. They thought they were of great significance as an etiological factor in carcinoma of the endometrium.

Our own experience with carcinoma of the endometrium in young women at Cook County Hospital is rather meager. The ones we see are mainly in older women in the far-advanced stages of the disease.

DR. JOHN I. BREWER, Chicago, Ill.—Not enough attention has been paid to the fact that ovulation may and actually does occur, and that portions of the endometrium not involved in the cancer respond in a perfectly normal fashion to ovarian stimulation. It means that endometrial cancer may occur in patients without evidence of hyperestrinism.

I do not believe that we are correct in casting aside such findings. The authors themselves noted it and mentioned it, and in numerical fashion described it.

They stated that they found six fresh ovulations in thirty-eight patients. If one operates upon normal menstruating women irrespective of the cycle, one would not expect to find fresh ovulations in a much higher incidence than in six out of thirty-eight. The most one would expect in thirty-eight patients, would be nineteen functioning corpora luteum if the cycles were normal and if the latter half of the cycle was chosen electively as the time to operate.

While ovulation may not be too common, it does occur, and it seems to me it occurs with sufficient frequency to be of significance. The fact that ovulation does occur, and that the endometrium not involved in the cancer responds in a perfectly normal fashion, means something. It suggests very strongly that hyperestrinism is not the sole important factor in the development of endometrial carcinoma. It means that endometrial cancer can occur and does occur in patients who have a completely normal ovarian hormonal balance and function.

DR. MICHAEL BOLEY, Chicago, Ill.—I am very glad to hear the essayists mention and reiterate that carcinoma of the endometrium in a menstruating woman is not the medical monstrosity which we have been taught it was.

At our tumor clinic at the University of Illinois we have had the opportunity to find this to be true. Our complete statistics as yet are not ready for publication.

Crossen has brought out several times that the woman who continues to menstruate after the age of fifty has a higher incidence of corpus carcinoma. Bear that in mind. About fibrosis uteri and/or the so-called benign menorrhagia of the preclimacteric, as one of the discussants mentioned, if you wish to treat this with radium, do not give small amounts of radium—give plenty of radium. We have always felt that a goodly amount of radium, as mentioned by Dr. Schmitz, is important, so that if these patients do begin to bleed at least you know where you are. We have given it and have felt we have done these patients good service. It is well to remember that a thorough curettage should precede the application of radium.

Again, in our own offices we can do the things that some of us forget we can do, notably, endometrial biopsy. I think probably there will be 70 to 75 per cent of the endometrial carcinomas that can be accurately diagnosed by a carefully done endometrial biopsy in your own office. If you feel the endometrial biopsy has not brought out sufficient tissue to make a proper diagnosis, and if you think there is a case of carcinoma clinically, then do a thorough curettage. You save time and money, and you save the patient grief.

DR. DOCKERTY.—I am glad that Dr. Schmitz agreed that we had indirect evidence for chronic hyperestrogenism in some of these patients. We did not want to lean over backward in stressing the importance of this, because, as I said, suppose we did not perform any bio-assays and we were not sure how much estrogens these patients were excreting.

We have presented other evidence in regard to hyperestrogenism. In a series of feminizing ovarian neoplasms, our incidence of carcinoma of the corpus uteri is about 20 per cent. These tumors are known to produce estrogen, and the uteri of these women contain fibroids in approximately 50 per cent. Many noted amenorrhea with definite suppression of ovulation.

On the other hand, I am very glad that Dr. Brewer brought up the opposing notion, namely, that women can have cancer of the endometrium when, apparently, from the clinical story, biopsy of the endometrium, and appearance of the ovaries, they are still ovulating and producing progesterone.

As far as treatment is concerned, I do not wish to quarrel with Dr. Schmitz about this. I do not know just exactly what should be the treatment for carcinoma of the corpus. However, I must say I am extremely happy that our group did not treat all of these patients with radium, otherwise I would not be on this platform presenting the pathologic material from thirty-three of these interesting cases.

Regarding the question of nodes, actually we did not find any nodes on the specimens. There were two cases which had recurrence in the pelvis and no doubt, in these instances, there was nodal involvement terminally. However, in checking over the removed uteri of those cases it was found that recurrence apparently obtained on the basis of peritoneal involvement at the time of operation. I am sure you are all familiar with the fact that carcinoma of the corpus uteri is a relatively benign disease until the peritoneum is breached. In my experience the lesions which have not penetrated deeply will not show nodal involvement. This is in contradistinction to the condition obtaining in the cervix.

Regarding the question of certain pale "interstitial" cells in the ovaries, I may say that we found them but did not know how to interpret them. Special fat stains showed some of these elements to be positively stained in some cases and not in others.

I am in favor of endometrial biopsy. We have shown that cancer of the uterus can occur in these young women. To omit this important procedure results in missing the diagnosis of carcinoma in the early curable stages. Curettage is particularly indicated if the individuals are suffering from irregular bleeding, and especially if they are obese and hirsute, or if they have diabetes and suffer from periods of amenorrhea. Vaginal smear studies may also be very helpful in this regard.

The difference in the accepted 6 per cent incidence for cancer of the corpus in young women and our figure of 2 per cent shows that our criteria for diagnosis are rather strict. We will not make the diagnosis of uterine cancer until it is bona fide cancer. We did not include in this series any case with so-called pink-staining glands or carcinoid hyperplasia. We recognize those changes and we call them benign.

DR. LOVELADY (Closing).—In answer to Dr. Lash's question, those patients with periods of amenorrhea also had minimum menorrhagia. This caused them to be investigated. Lymph gland involvement I shall leave for Dr. Dockerty to discuss.

I agree that more extensive glandular dissection may be carried out with probably little increased risk to the patient.

In answer to Dr. Brewer, I agree that carcinoma of the corpus can occur without excess estrogen, but if the set-up is right in the patient, the carcinogenic factor of the estrogenic hormone cannot be overlooked.

One should stress early recognition by the patient and physician alike. Perhaps we have not paid enough attention to those patients who are obese and who have marked hirsutism, etc. It is only by a careful history and physical examination and, in doubtful cases, hormone assays, that we are able to determine the necessity for estrogenic therapy. From the evidence we have at hand, the injudicial use of estrogenic therapy in large and prolonged administration should be condemned.

ANTICOAGULANT THERAPY IN GYNECOLOGIC SURGERY*

BENJAMIN E. URDAN, M.D., F.A.C.S., AND MARVIN WAGNER, M.D.,
MILWAUKEE, WIS.

(From the Departments of Gynecology and Obstetrics, Marquette University and Mount Sinai Hospital)

WITH the advent of modern methods of anesthesia, the use of antibiotics, and the more comprehensive attention to electrolyte and fluid balance, the morbidity of the surgical patient has markedly decreased. However, the danger of intravascular clotting with its possible pulmonary embolus still persists, and remains one of the dreaded complications of gynecological surgery.

Previously, when a patient died of a pulmonary embolus, many believed that the death was unavoidable. However, our present advances make us wonder whether or not sequelae from intravascular clotting such as thrombophlebitis, phlebothrombosis, or even death from a pulmonary embolus should not be classified as preventable. As Allen[1] so aptly recorded in his paper: "It is timely to consider that blood may normally clot too well to serve the best interests of the health of man. The protective device provided by nature is actually harmful as well as protective. Nature has provided not wisely but too well." By nature, the power of coagulability is one of protection as well as that of actual harm.

Fortunately, in our present day, the profession has added to its armamentarium anticoagulant therapy, and it is with one of these preparations, namely, Dicumarol or 3,3′-Methylenebis (4hydroxycoumarin), that this paper is concerned. The pharmacological effect of this drug is to lengthen the prothrombin clotting time by decreasing the prothrombin level of the blood. Prothrombin is recognized only by its ability to clot blood after it is converted to thrombin. As can be seen in Fig. 1,[2] in the mechanism of blood clotting, any interference with the existence of prothrombin would result in no clot formation.

Since our use of Dicumarol is so dependent upon the prothrombin time, it is of the utmost importance that a test be employed for the determination of prothrombin activity which would be efficacious but still not too burdensome. There are varied tests for this determination of prothrombin activity; for example, the two-stage method of Warner, Brinkhause, and Smith, as well as Quick's[7] one-stage method. However, we feel these are too cumbersome for daily clinical use.

We have employed the "simple bedside test" of Ziffren, Owen, Hoffman, and Smith,[3] which is carried out with whole blood the moment it is drawn. The only reagent needed for this test is thromboplastin. This test also employs

*Read at the Eighteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Milwaukee, Wis., Sept. 21, 22, and 23, 1950.

a normal control which permits one to express results in reference to a normal standard. This means expressing the results in percentage of 100 and is preferable to expressing the prothrombin time in seconds.

Patients vary in their sensitivity to Dicumarol for its effect depends, to some extent, on the rate of absorption, the state of nutrition, and the body weight. The safe and effective degree of prothrombin deficiency produced by Dicumarol lies in a comparatively narrow zone; namely, when the concentration of prothrombin in the blood is between 10 and 30 per cent of normal. Allen, Barker, and Hines[4] have recorded in their experience of a large number of surgical cases that thrombosis in human beings is almost certainly inhibited if the level of prothrombin in the plasma is less than 30 per cent of normal; and serious bleeding almost certainly will not occur if the level of prothrombin is greater than 10 per cent of normal. The prerequisites for adequate Dicumarol therapy are a reliable experienced laboratory, prothrombin time determinations taken daily or at least every two days, and individualization of each patient.

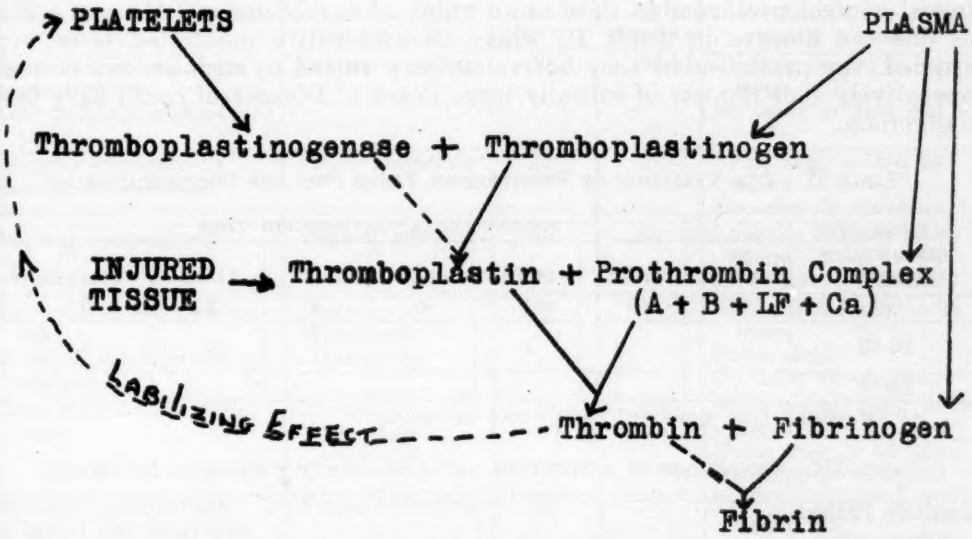


Fig. 1.—Coagulation mechanism. Broken lines indicate catalytic or enzymatic action.

Material

We have made a clinical survey of 900 consecutive major gynecological postoperative cases, in 450 of which Dicumarol was given routinely as a means of preventing any untoward complications from intravascular clotting. These patients were operated upon by the senior author, while the patients who were not given Dicumarol were operated upon by both gynecologists and general surgeons. Parenthetically, may we add that it was not our endeavor to substitute anticoagulant therapy for early ambulation, since this was routinely employed in the entire series of 900 cases.

Dicumarol is administered in the form of a tablet, each containing 100 or 50 mg. of the drug. The entire 24-hour dose is administered orally at about the same hour every day. Our plan of dosage is dependent upon what we term

the control prothrombin time which is the value ascertained on the morning of the first postoperative day. All subsequent prothrombin times are taken at about the same hour daily. As can be observed in Table I, the initial prothrombin time in different individuals is quite variable.

TABLE I. INITIAL CONTROL PROTHROMBIN TIME VARIATION IN PATIENTS

PER CENT OF NORMAL	NUMBER OF PATIENTS
100	189
90 to 99	42
80 to 89	87
60 to 79	111
50 to 59	21

If our value is 100 per cent of normal we begin with an initial dose of 300 mg. of Dicumarol. If the control prothrombin time is between 60 and 80 per cent of normal, our initial dose is 150-200 mg. of the medication. Finally, if the value is below 60 per cent of normal, we proceed with caution, administering 100 mg. or less of the drug initially.

It has also been interesting to observe that a patient's prothrombin time usually rises after surgery and bears out the importance of employing the initial control prothrombin time as an index of our Dicumarol therapy. For, as one can observe in Table II, where 25 consecutive unselected cases were studied, the prothrombin time before surgery varied to such an extent postoperatively that the use of initially large doses of Dicumarol could have been dangerous.

TABLE II. THE VARIATION OF PROTHROMBIN TIMES PRE- AND POSTOPERATIVELY

PREOPERATIVE PROTHROMBIN TIME*	POSTOPERATIVE PROTHROMBIN TIME						
	NO CHANGE	95-91	90-85	84-79	78-72	71-68	67 AND BELOW
100	1	3	1	6	4	2	1
90-80			1		1	2	2 (64, 60)
79-70							1 (61)

*Prothrombin time expressed as per cent of normal.

TABLE III. COMPARISON OF A SENSITIVE AND A RESISTANT PATIENT TO DICUMAROL

Sensitive Patient.—															
Postoperative day					1			3			5			8	
Prothrombin time (% of normal)					100			20			40			Dismissed	
Dicumarol dosage (mg.)					200										
Resistant Patient.—															
Postoperative day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Prothrombin time (% of normal)	100	77	65	50	48	60		81	86		81	65	60	50	60
Dicumarol dosage (mg.)	300	100	100	100	50	100	100	200	200	100	100	100	100	50	
					Positive Tender calf Homan's sign						No tenderness or Homan's	Out of bed		Home	

As we have previously emphasized, individualization is a very essential factor in Dicumarol therapy. Allen[4] noted that less than 5 per cent of patients appear to be resistant to the drug. Also, there are patients encountered who

are sensitive to Dicumarol, and whose concentration of prothrombin in the blood may fall abruptly to less than the critical level with just the initial dose of this drug. In Table III, we cite two cases. One patient illustrated marked sensitivity to the drug, experiencing a profound rise in the prothrombin time after receiving only 200 mg. of Dicumarol; whereas, the other patient seemed to be refractory to the drug, having received 1,700 mg. of Dicumarol over a period of 15 days with an ultimate prothrombin time of 50 per cent of normal.

We maintain the prothrombin deficiency in our patients between the level of 30 to 40 per cent of normal until they have become totally ambulatory for three days. The patient is not kept in bed longer than she would be if she were not on Dicumarol therapy. Before dismissal of the patient, a check prothrombin time is taken to be sure that a rise to normal is taking place.

TABLE IV. RESPONSE TO VITAMIN "K" THERAPY ON BLEEDING HYPOPROTHROMBINEMIC PATIENTS

TYPE OF POSTOPERATIVE CASE	CLINICAL MANIFESTATIONS OF BLEEDING	PROTHROMBIN TIME (% OF NORMAL)		CLINICAL COURSE AFTER VITAMIN K THERAPY
		DAY OF BLEEDING	24 HOURS AFTER VITAMIN K THERAPY	
Subtotal hysterectomy Appendectomy Left Salpingo-oophorectomy	Vaginal bleeding	30	60	Bleeding ceased in 12 hours No delay in dismissal
Subtotal hysterectomy Bladder advancement	Frank hematuria	26	52	Urine clear within 24 hours No delay in dismissal
Vaginal hysterectomy	Vaginal bleeding	30	60	Bleeding stopped in 10 hours No delay in dismissal
Total abdominal hysterectomy Bilateral salpingo-oophorectomy	Melena Microscopic hematuria	37	54	Stool normal color in 24 hours Urine clear No delay in dismissal
Total abdominal hysterectomy	Melena Microscopic hematuria	10	29	Stool normal color in 30 hours Urine clear in 24 hours No delay in dismissal
Subtotal hysterectomy Bilateral salpingo-oophorectomy	Vaginal bleeding	24	56	Bleeding ceased in 8 hours No delay in dismissal
Subtotal hysterectomy	Vaginal bleeding	19	36	Bleeding stopped in 12 hours No delay in dismissal

The only hazard accompanying the use of Dicumarol is the possibility of hemorrhage. In our series we have encountered seven cases of bleeding which we attributed to over-Dicumarolization (Table IV). As can be seen, by the employment of 72 mg. of menadione sodium bisulfite (Hykinone) intravenously, and 30 mg. of Synkayvite intramuscularly three times at four-hour intervals, bleeding ceased and the prothrombin time was out of the realm of the critical level within 24 hours. In fact, on several occasions, we found a response within four hours.

If, however, an excessive hypoprothrombinemia should occur without a satisfactory response to synthetic Vitamin K, Cosgriff and his associates[5]

recommend lyophilized plasma. Also whole blood transfusions have been used with adequate effect; however, in this series, we have had no occasion to use plasma or whole blood.

There are certain definite contraindications to Dicumarol therapy.[8] The absolute are: hemorrhagic diseases, significant liver disease, moderate to severe renal disease, subacute bacterial endocarditis, and conditions in which patients are being submitted to tube drainage. The relative are: dietary deficiency states, especially of vitamin K, fever, salicylate or sulfonamide therapy, and operations on the brain and spinal cord.

Allen,[1] in his conclusion of a survey of 1,686 cases, noted that approximately 73 lives were saved by the use of Dicumarol and that 211 patients were spared the experience of venous thrombosis and pulmonary embolus.

Wise and associates[6] made a four-year survey of 3,304 cases in which Dicumarol was used prophylactically following major surgery. They recorded the following statistical results: 35 of 2,030 (1.6 per cent) of untreated cases had vascular complications.

As can be seen in Table V, in the 450 patients not treated with Dicumarol there were 31 complications from intravascular clotting. This included 7 cases of phlebothrombosis, 11 cases of thrombophlebitis, 9 cases of pulmonary embolism with infarction, and 4 cases of fatal pulmonary embolism. In the comparative group of 450 cases, there was only one vascular complication (Table III), this being the case of the individual who was refractory to Dicumarol and who developed phlebothrombosis.

TABLE V. TYPES OF CASES WITH THROMBOEMBOLIC COMPLICATIONS (NO DICUMAROL)

TYPE OF OPERATION	PHLEBO-THROMBOSIS	THROMBO-PHLEBITIS	NONFATAL PULMONARY EMBOLUS WITH INFARCTION	FATAL PULMONARY EMBOLUS
Vaginal plastic	2	1	2	
Salpingo-oophorectomy with appendectomy	2	2	3	
Salpingo-oophorectomy	1	1	2	
Total abdominal hysterectomy	1	2		1
Subtotal hysterectomy	1		2	
Laparotomy and subtotal hysterectomy plus vaginal plastic		1		1
Umbilical hernia plus vaginal plastic		1		
Pelvic laparotomy; hysteropexy		1		
Lysis of adhesions		1		
Ventral hernia		1		1
Myomectomy				1
Total	7	11	9	4

Comment

It is well appreciated by the authors that the non-Dicumarolized patients were operated upon by various surgeons, and, consequently, preoperative preparation, technique, and modes of handling tissue were at variance with the methods used by the senior author who operated upon the Dicumarolized patients.

It would have been ideal to have had a comparative study of the results of one surgeon. However, we feel that this study illustrates that in a private or general hospital, where there is always variance of technique and treatment of operative patients, the employment of Dicumarol therapy prophylactically can be safe, and will decrease the incidence of, or entirely eliminate, intravascular clotting and the sequelae of this dreaded complication.

TABLE VI. SUMMARY OF THE TYPES OF CASES SURVEYED

TYPES OF CASES ANALYZED	DICUMAROLIZED PATIENTS	NONDICUMAROLIZED PATIENTS
Subtotal hysterectomy and/or salpingo-oophorectomy and/or appendectomy	190	189
Vaginal hysterectomy	37	20
Vaginal plastic, bladder advancement, perineorrhaphy, enterocele	110	125
Total abdominal hysterectomy	55	20
Laparotomy and vaginal subtotal hysterectomy, appendectomy, vaginal plastic, salpingo-oophorectomy	14	20
Salpingo-oophorectomy and appendectomy or presacral neurectomy	44	48
Hysteropexy		20
Vaginal plastic and myomectomy or fundectomy		8
Total	450	450

Summary

A clinical survey of 900 consecutive, postoperative gynecological cases, in 450 of which Dicumarol was given routinely as a means of preventing any untoward complications from intravascular clotting has been presented.

Plan of dosage was dependent upon the control prothrombin time, which is defined as the value ascertained on the morning of the first postoperative day. The control prothrombin time has proved an excellent index for safe and efficient Dicumarol therapy, as was illustrated in sensitive and resistant patients to the drug, in the preoperative and postoperative variations of the prothrombin time, as well as the variation in the initial prothrombin time in different individuals.

The simple bedside test of Ziffren for prothrombin activity is an ideal procedure for Dicumarol therapy. A reliable experience in laboratory tests and individualization of patients are of prime importance for adequate and safe treatment.

In 450 Dicumarolized postoperative patients, there were 7 cases of hypoprothrombinemia with consequent bleeding which was readily controlled by vitamin K therapy; however, there was one case of phlebothrombosis in an individual who was refractory to this therapy.

In 450 comparable, non-Dicumarolized patients, there were 7 cases of phlebothrombosis, 11 cases of thrombophlebitis, 9 cases of nonfatal pulmonary embolism, and 4 cases of fatal pulmonary embolism.

References

1. Allen, E. V.: J. A. M. A. **134**: 323, 1947.
2. Quick, A. J.: Personal communication, Mechanism of Blood Clotting Lecture, Marquette University, Milwaukee, Wis.
3. Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P.: Am. J. Clin. Path., Tech. Supp. **4**: 13, 1940.
4. Allen, D. V., Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, Philadelphia, 1947, W. B. Saunders Company, pp. 730-738.
5. Cosgriff, S. W., Cross, R. J., and Habif, D. V.: J. A. M. A. **138**: 405, 1948.
6. Wise, W. D., Loker, F. F., and Brambel, C. E.: Surg., Gynec. & Obst. **88**: 486, 1949.
7. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., 1942, Charles C Thomas.
8. Meyer, O. O.: Wisconsin M. J. **49**: 385, 1950.

425 EAST WISCONSIN AVENUE

Discussion

DR. PAUL F. FLETCHER, St. Louis, Mo.—In gynecological surgery, the factors which predispose to the development of thrombophlebitis are principally trauma and infection because chemical injury to the vascular endothelium rarely if ever occurs. Phlebothrombosis occurs as a result of venous stasis rather than because of alterations in the constituents of the blood.

When endothelial trauma is responsible for the development of a venous thrombus it is logical to assume that the original clot is well established before the initial control prothrombin time of the authors is determined. Dicumarol prevents the further development of thrombi but, of course, has no effect upon the initial intravascular clot.

Early ambulation, when started within 24 hours after operation seems to us to be a better routine procedure than prophylactic Dicumarol therapy, because it requires less time and effort on the part of trained hospital personnel and involves fewer potential complications. It is an excellent safeguard for phlebothrombosis and a highly commendable factor in the routine prophylaxis of thrombophlebitis if it is started within the first 24 hours. The authors did not say how soon it was started in their cases.

When infection is a factor in the development of thrombophlebitis, a morbid process must be present before endothelial injury with consequent thrombus formation can ensue. Since thrombophlebitis is only one of several complications that might result from postoperative sepsis, methods directed toward the control or prevention of infection may be more tenable as a routine procedure than the use of Dicumarol.

In a recent publication[1] we reported results obtained from the routine use of vaginal suppositories containing 200,000 units of calcium penicillin. The incidence of morbidity in this series was 5.5 per cent as compared to 30 per cent in the control group. Our criterion for morbidity was a temperature of 100.4° F. or higher on any two postoperative days beginning 24 hours after operation. To date they have been used routinely in 361 consecutive gynecological cases, in none of which has there been any type of vascular complication. The number of hospital days required for postoperative convalescence was reduced appreciably and the cost of hospital care was not increased. These suppositories are available, commercially, under the trade name of Pelvicins.

It is noted that the authors reported seven cases of hypoprothrombinemia with consequent bleeding, an incidence of 1.55 per cent. The incidence of vascular complications in their control group was 6 per cent and in the series of 2,030 untreated cases reported by Wise and his associates the incidence of vascular complications was 1.6 per cent.

We think early ambulation, started within the first twenty-four hours after operation, and the control of morbidity have more significance as routine postoperative procedures and involve less potential complications than the routine use of Dicumarol.

The incidence of vascular complications increases with age. It is highest in patients over 50 and seldom occurs under 40. Some of the more common predisposing factors are dehydration, extensive varicosities, heart disease, obesity, and unavoidable trauma at the time of operation. Therefore it is our belief that Dicumarol postoperatively, should be used only for those patients who have a better-than-average chance of developing either thrombophlebitis or phlebothrombosis.

I think the authors have made an excellent contribution to gynecologic surgery. Their results have been carefully compiled and very well presented. They have included a variety of operative cases. Of the 259 hysterectomies, 204 were supracervical and 55 complete. In the control group 209 were supracervical and 20 complete. This is of interest to us because in our "neck of the woods" it is perhaps the exceptional case in which the cervix is not removed.

1. Fletcher, Paul F.: South. M. J. 43: No. 8, August, 1950.

DR. RALPH A. REIS, Chicago, Ill.—This review stimulated me to comment on the comparison of the two groups.

The senior essayist is a finished gynecologic surgeon. I have had the opportunity of seeing him work repeatedly and I know what fine work he does. When he has compared his 450 patients with the 450 done by general surgeons, and he has shown that the 450 patients done by general surgeons had eighteen vein complications and fourteen pulmonary emboli which I am sure is more than he has encountered in his entire career and more than I have had in thirty years of practice, I believe that the conclusion of this study would be not that Dicumarol is a good prophylactic against venous complications but that the best prophylactic against venous complications is a thorough, well-grounded training in gynecologic surgery.

DR. URDAN (Closing).—I agree with Dr. Fletcher that the possibility of endothelial injury is one of the many causes of phlebothrombosis and thrombophlebitis. However, no therapy directed at one or all of these supposed causes has reduced the incidence of intravascular clotting except the use of the anticoagulants. With regard to the fact that intravascular clotting can occur before the Dicumarol takes effect, Dr. Quick has recently shown that there is a prothrombin complex that is exceedingly susceptible to the action of Dicumarol within a comparatively short time. (Quick, A. J.: Surg., Gynec. & Obst. 91: 296, 1950.)

I agree that the incidence of almost 7 per cent of complications in the so-called control group is very high. This is about twice the expected number. We stated that it would have been ideal if we had had a control series of our own. We felt preoperative preparation, indication for operation, the type of operation performed, the mode of handling tissues, sutures, and so on undoubtedly played a great role in the incidence of an almost 7 per cent complication in this so-called control series.

With regard to the high number of subtotal hysterectomies, we follow the so-called trend of today, in which we do many more totals, about four totals to one subtotal; but in this series we were trying to keep as close a comparison as was possible.

There was one statement I want to read to you which lack of time did not permit presenting in the original paper. This is a résumé of a paper which was published by McCann, in the *New England Journal of Medicine*, February, 1950, No. 6, which is entitled "Thrombo-Embolism." It is a four-year study of 2,354 cases, all of which were routinely Dicumarolized for the purpose of controlling postoperative thromboembolism. McCann states that the incidence of thrombosis was a fairly constant figure of about 2.5 per cent with ten days of bed rest or with ambulation on the first to the third day; and, incidentally, in our 900 cases all patients were ambulated on the first postoperative day.

All of McCann's patients had supplemental use of position, exercises, and circulatory stimulation. Thirteen cases of thromboembolism were encountered in patients permitted ambulation from the first to the third postoperative day. Usually one or two deaths from massive embolism occurred every year. One died from massive embolism on the fifth postoperative day, although she had been ambulated the morning after surgery.

When Dicumarol was administered prophylactically, the rate of thromboembolism dropped sharply to 1.5 per cent, with no deaths from embolism.

As we stated, with careful watching, a good laboratory and a good, efficient resident who will watch the reaction of these patients to Dicumarol carefully, the complications and the danger of hypoprothrombinemia, with consequent bleeding, are practically minimal.

HORMONE SECRETION BY HUMAN PLACENTA GROWN IN THE EYES OF RABBITS*†

H. L. STEWART, JR., M.D., DETROIT, MICH.

(From the Department of Obstetrics and Gynecology and The Edsel B. Ford Institute for Medical Research, Henry Ford Hospital)

SUCCESSFUL growth of human placenta in tissue culture in a previous study showed that the Langhans cells secreted gonadotropin.[1] The amount of gonadotropin in the tissue culture fluid was directly proportional to the number of the Langhans cells present. Syncytial cells grew sparingly and degenerated early. The study was inconclusive as to the production of estrogens and progesterone due to the failure of syncytial cells to grow.

Since estrone, progesterone, and their metabolic derivatives attain the highest concentrations in the blood and urine during the last month of pregnancy, it would be desirable to grow the full-term placenta. In all attempts, tissue cultures of the term placenta were unsuccessful, and resulted only in an overgrowth of fibrous elements. Syncytial cells, as well as Langhans cells, failed to grow.

Intraocular transplants in monkeys, guinea pigs, hamsters, and rabbits have been successful in the study of normal tissues of the male and female genital systems, as well as embryonic organ implants and benign and malignant tumors. Implantation of the mature human placental tissue into the eyes of rabbits offers a method of study where tissue cultures in vitro have been inconclusive. If Langhans cells are present in the term placenta, will they grow in intraocular explants with evidence of gonadotropin secretion? Will syncytial cells grow with evidence of estrogen and progestin secretion? The present study developed with these questions in mind.

Method

Placental tissues were obtained under aseptic conditions from term pregnancies at the time of cesarean section. Cases were selected when delivery by the abdominal route was indicated for disproportion prior to the onset of active labor. Large portions of the placenta were selected to avoid drying and placed in sterile Petri dishes for immediate transfer to the laboratory. Small pieces, measuring approximately 0.5 mm., were immediately implanted into the eyes of rabbits. When decidual implants were performed the tissue was obtained by a sharp curette under direct vision selectively removed from the placental site. Histological examination was made of the placenta and decidua from which the implants were obtained.

Forty-two adult female rabbits weighing 1,500 to 2,000 grams were used. All animals were isolated in separate cages at least three weeks prior to use and throughout the study. When castrated animals were used, the ovaries were removed two weeks prior to the explant operation. The animals were

*Read at the Eighteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Milwaukee, Wis., Sept. 21, 22, and 23, 1950.

†Annual Prize Award paper.

observed as to their general nutritional state. As a rule only one eye was used in each animal, but in a few cases where the tissue regressed to a small fibrous area, the opposite eye would be utilized for a second explant. A total of forty-eight explants was achieved.

While the possibility of transplanting tissue into the eye of experimental animals has long been known, it has not been widely practiced because of its technical difficulties. The rabbits were anesthetized by an ether cone with the animal confined in a rabbit box and the head exposed. Supplemental use of local anesthesia reduced the amount of ether required. The eye instruments used were: lid retractor, keratome, sclera forceps, and probe. A small incision was made with the keratome at the corneoscleral junction, which permitted as little loss as possible of fluid from the anterior chamber of the eye. By means of a probe, the tissue was easily and quickly deposited well away from the incision and between the iris and the cornea. For a reason which is discussed later, the tissue was not placed in the most dependent portion of the anterior chamber. It was very easy to err by attempting to transplant large pieces of tissue. Sutures were not necessary to close the incision. No postoperative care of the eye was necessary as primary healing of the incision was the rule. Observations of the vascularization and growth of the implant were frequently made.

The ovaries and uterus of the rabbit were examined for evidence indicating biologic activity of the explants. Under ether anesthesia, the abdominal wall was shaved and a small incision provided sufficient exposure for examination of the genital organs. Silk suture closures were used. Examinations were repeated at intervals of one or two months. Microscopic sections of all tissues removed were studied. The eye sections included the cornea, occasionally the iris, and the growth in the anterior chamber. Photographs were made of the eye, uterus, and ovaries.

Results

Approximately 20 per cent of the forty-eight explants failed to show gross evidence of growth. Small areas of local necrosis occurred, but infection was not a cause of failure. By the end of the fourteenth day evidence of a "take" was apparent. The growth was clean, but the edges were not well defined due to growth projections. Vascularization was evident within another week. By means of a hand lens, progress of growth was easily discernible. In cases of rapid growth distortion of the iris and cornea would occur.

Operative trauma of the eye was minimal and no evidence of immediate hemorrhage was noticeable after the technique was perfected. Hematomas were rare. In several cases, about thirty-six to forty-eight hours after operation, a small collection of bright red blood was noted in the most dependent portion of the anterior chamber of the eye. A logical assumption would attribute this to the presence of small amounts of heparin in the placental tissue. In order to observe this phenomenon, explants were placed at higher levels rather than in the most dependent portion of the chamber.

Since there was evidence of growth of the explants, attention was next directed to the individual cellular elements. In our previous study with tissue cultures of the early placenta, it had been established that the Langhans cells secrete gonadotropin.[1] Are these cells present and growing in the explants of the mature placenta? The presence of corpora hemorrhagica and corpora lutea in the ovaries of the test animals would be suitable criteria of the presence and growth of Langhans cells. This would be valuable evidence in the controversial issue as to the presence of the Langhans cells in the term placenta.

There were eight successful intraocular explants of mature placental tissue in test animals with intact ovaries and uterus. All exhibited growth on gross examination as well as biologic activity. Period of observation extended from four to six months. The course of events among animals in this group is exemplified in the Protocol of Rabbit No. 2.

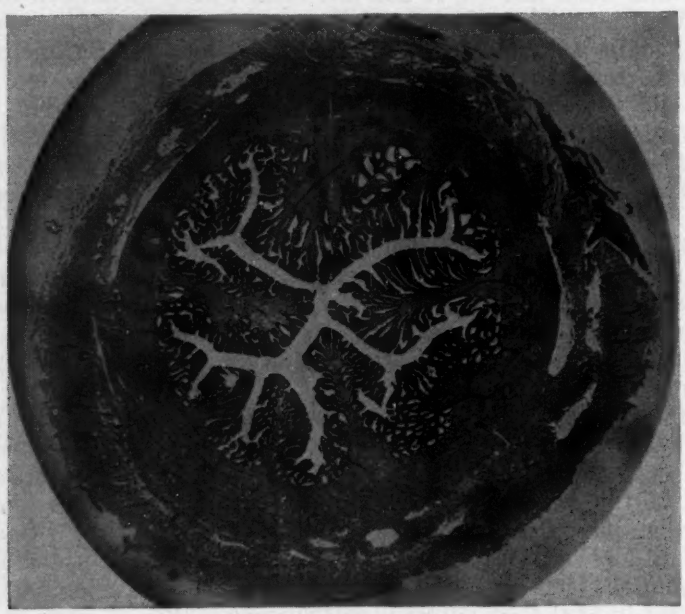


Fig. 1.—Photomicrograph. Progestational changes were evident in the uterus of Rabbit No. 2. (×16.)

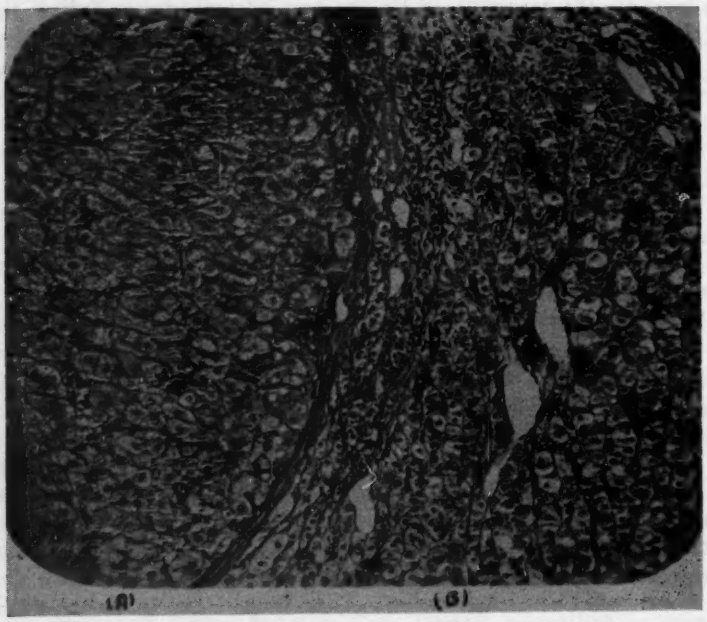


Fig. 2.—Photomicrograph of ovarian tissue from Rabbit No. 2 shows a well-formed corpus luteum (A) with an overgrowth of interstitial cells (B). (×100.)

Protocol Rabbit No. 2.—

The tissue was implanted in the right eye of this rabbit on Dec. 30, 1946. Growth was excellent.

After an interval of four weeks, the peritoneal cavity was opened under ether anesthesia. Large follicles, corpora hemorrhagica and corpora lutea were clearly seen. The uterus was greatly enlarged and reddened.

At the end of twelve weeks a laparotomy was again performed and similar findings were present as compared with the fourth-week examination.

The animal was sacrificed at the end of the eighteenth week. The uterus was large and red. Sections of the uterus showed progestational development (Fig. 1). There was marked enlargement as compared to the uterus of a castrated rabbit. Ovarian sections showed well-developed corpora lutea with a marked overgrowth of interstitial cells (Fig. 2). The eye growth had greatly enlarged from a few cells to a large, well-vascularized structure (Fig. 3). Photomicrographs of the villuslike projections of the placental growth in the eye showed both Langhans and syncytial cells (Fig. 4).

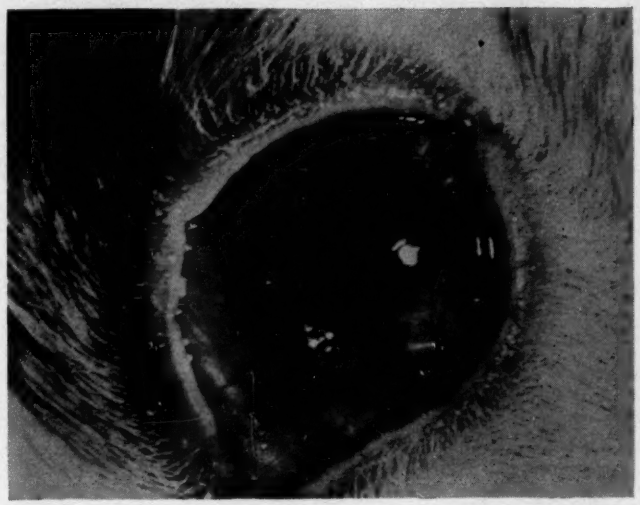


Fig. 3.—Photograph of the eye of Rabbit No. 2 at the end of the eighteenth week. The placental tissue has grown from a small implant measuring 0.5 mm. to a large, well-vascularized growth.

These results strongly favor the presence and growth of the Langhans cells in the mature placental explants. Not only was growth by histologic examination evident, but biologic activity as well. Although syncytial cells were present by histologic examination, biologic activity remained to be demonstrated.

A control series of animals with intraocular explants of decidual tissue was used. The first laparotomy at the end of the fourth week surprisingly revealed a large uterus and corpora hemorrhagica and lutea in both ovaries. The genital tract development was similar to that produced by the placental explants in Rabbit No. 2. The eye growth enlarged, but at the end of the eighth and twelfth weeks regression of the uterine growth had occurred and ovarian response was no longer evident. This was in marked contrast to the biologic responses of the placental growths. Obviously the selection of decidua as a control tissue was a poor one. The initial response to the intraocular decidual explants was one of absorption. This reaction supports the findings of others that the chorionic gonadotropin is present in the endometrium during pregnancy.

Additional control series consisted of endometrial and myometrial implants from nonpregnant women. There were no uterine or ovarian responses in any of these animals. Placental tissues extracted with alcohol and ether gave negative responses. Alcohol extractions removed gonadotropins while estrogens are ether soluble. Placental anl decidual explants which failed to grow were permitted to regress to fibrous tissue islands and served as another control series. These were characterized by a weak initial response at the end of the fourth week due to absorption of the hormones without subsequent evidence of stimulation of the uterus or ovaries.

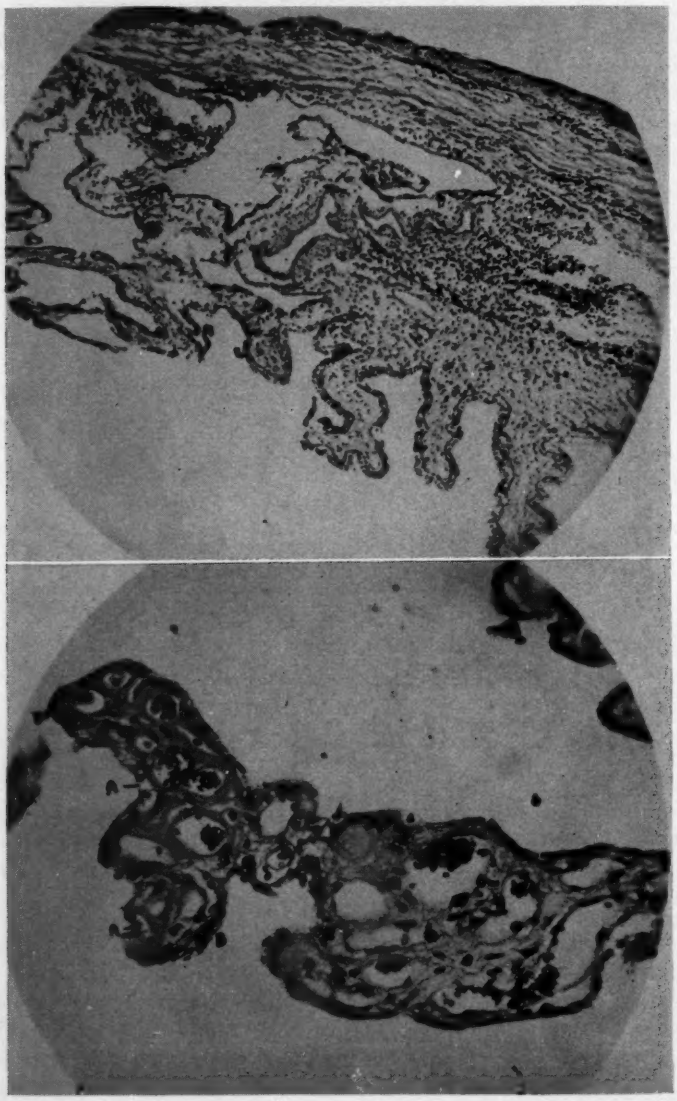


Fig. 4.—Photomicrographs showing growth of placental villi in the rabbit's eye (upper). (×50.) Higher power (lower) demonstrates Langhans cells (A) and collections of syncytial cells (B). (×430.)

Protocol Rabbit No. 14.—

This animal exemplifies the series of rabbits with intraocular implants of term placenta with evidence suggesting estrogen secretion. After the implants were well established and growing, the animals were castrated and uterine response noted.

Placental tissue was implanted into the eye on May 3, 1947. Growth was excellent during the next three weeks. At the end of the fourth week the first laparotomy revealed ovarian reaction and uterine enlargement similar to that of Rabbit No. 2. The animal was castrated.

At the end of the eighth week the uterus was smaller than on the first examination. Re-examination at the end of the sixteenth week revealed an enlarged and reddened uterus which was interpreted as evidence of estrogenic stimulation.

The animal was killed in the twenty-second week, or five and one-half months after the placental tissue was implanted. The uterus had continued to enlarge and microscopic examination showed a uterus similar to the one shown in Fig. 8.

Fig. 5.—Photomicrograph showing uterine growth at the end of the eighth week (Rabbit No. 22). (×16.)

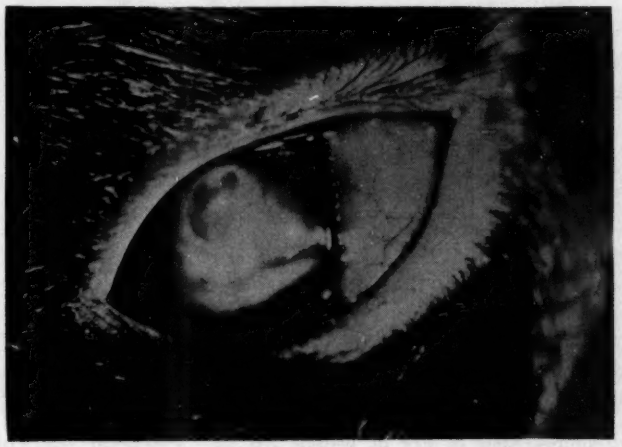


Fig. 6.—Photograph of placental tissue growth in the eye of Rabbit No. 22 at the end of 20 weeks.

Protocol Rabbit No. 22.—

Evidence of estrogenic secretion by placental growths would be more conclusive if uterine enlargement occurred in castrated animals.

The experimental findings in this animal illustrate a large group where the animals had been castrated three weeks prior to the explanation operation. It was more difficult to grow

the placental tissue in castrated rabbits and failures were more numerous than in rabbits with intact ovaries. Possibly the reciprocal action of the ovaries and the explant may be an important factor in the success of the intraocular growth.

The placenta was implanted in the eye of castrated Rabbit No. 22 on Oct. 24, 1947. The tissue grew nicely and soon vascularization was noted. The biologic activity of the explant was slow in its manifestations for at the end of the third week only slight uterine growth was perceptible.

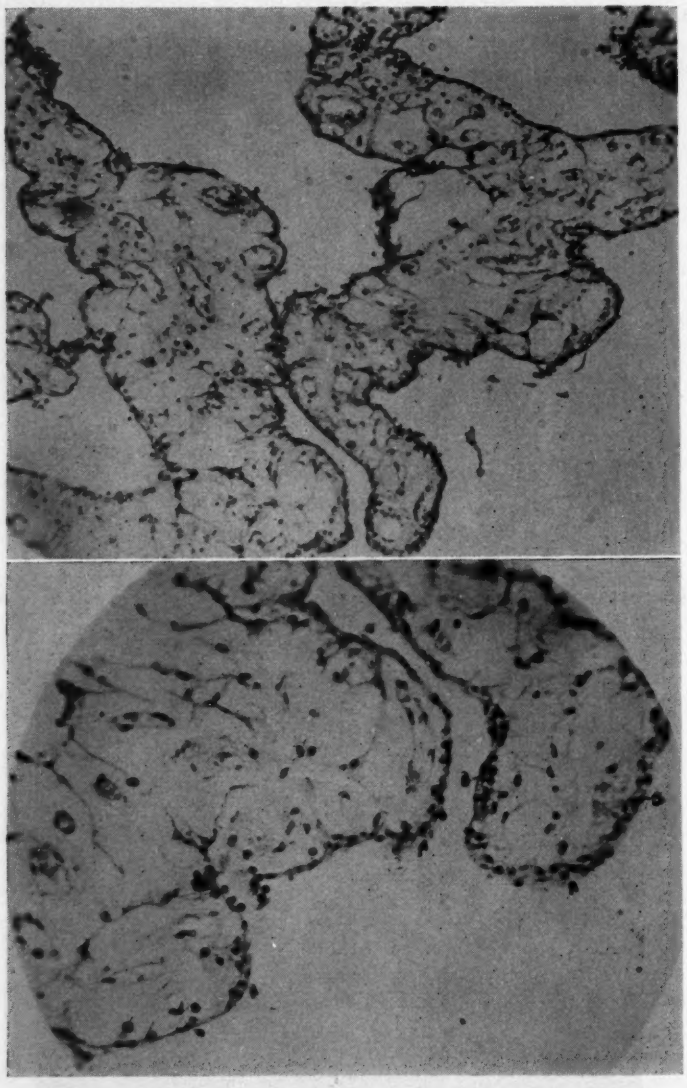


Fig. 7.—Photomicrographs of eye of Rabbit No. 22. Placental villi (upper) (×50) with higher power (lower) (×430) showing syncytial cells (A) and occasional Langhans cells (B).

Examination at the eighth week revealed a much larger uterus. Sections of the uterus were additional evidence of estrogenic development (Fig. 5). The eye growth was clean and well developed.

The sixteenth-week examination demonstrated still further growth of the uterus.

The rabbit was placed in a special cage for a twenty-four-hour period during the eighteenth week in order to collect urine for estrogen assay. Adult spayed female mice were injected subcutaneously twice daily for three days and vaginal biopsy on the fifth day revealed good estrogenic response.

A photograph of the eye explant prior to enucleation was made on the twentieth week. The original tissue implant had grown tremendously and had almost perforated the cornea. Surrounding this was a wide halo of new growth involving the greater part of the anterior chamber (Fig. 6). Section of the eye demonstrated villuslike growths containing syncytial and Langhans cells (Fig. 7). The uterus had undergone marked growth. The uterine sections showed estrogenic development without evidence of progestational changes (Fig. 8).

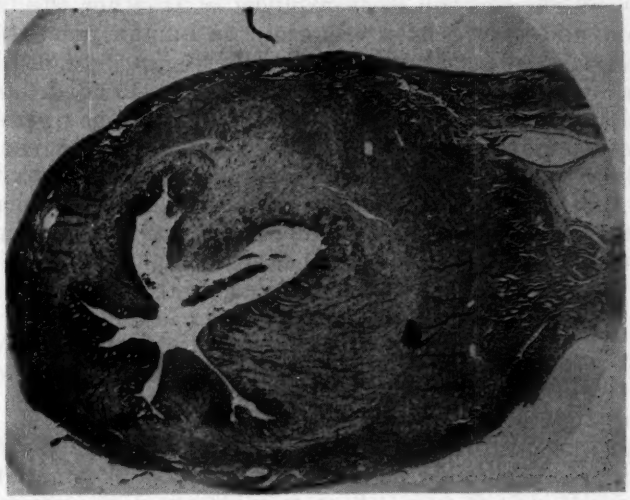


Fig. 8.—Uterus of Rabbit No. 22, showing marked estrogenic response at the end of the twentieth week. (×16.)

The rabbit was kept under observation until the twenty-fourth week or the sixth month. Regression of uterine growth was clearly defined. No difficulty was encountered with infection of the eye socket following enucleation.

Decidual implants into the eyes of castrated rabbits showed excellent local growth without demonstrable uterine growth. The slight amount of development early was believed due to absorption of estrogens present in the decidua during pregnancy.

Comment

In 1943, Jones, Gey, and Gey[2] presented the first direct evidence for the formation of gonadotropin by the Langhans cells. Growth of the Langhans cells from the placenta of early pregnancy in vitro in tissue cultures by Stewart, Sano, and Montgomery[1] confirmed their findings. These studies failed to establish the placenta as the site of formation of estrogens due to the failure of the syncytial cells to grow. Gonadotropin secretion is more abundant early in pregnancy while estrogen and progesterone curves of secretion reach a maximum peak late. Hence, ability of mature placenta to grow in tissue culture would be favorable for study of estrogen and progestin. Cells of the term or mature placenta failed to grow.

Since mature placenta does not grow in tissue culture, the study of hormone secretion cannot be complete by tissue culture alone. A logical approach to hormone secretion of mature placenta is by intraocular placental explants.

Therefore, this study is a continuation of the problem of hormone secretion by human placental tissue. Cells from the full-term placenta have been grown in the eyes of rabbits where in vitro tissue cultures have been unsuccessful. Consequently, evidence as to the secretory activity of the term placenta has been presented. It is accepted that the intact Langhans cell layer of the early placenta disappears after the third month, and the presence of these cells in the mature placenta has been questioned. This study has shown that Langhans cells were present throughout pregnancy and could be grown from the term placenta with evidence of secretion of gonadotropin.

For the first time syncytial cells from the human placenta have been grown. For the first time, syncytial cells have been shown to secrete estrogens. Here is direct evidence in the basic problem of whether the large quantities of gonadotropin and estrogens present in the human placenta during pregnancy are merely stored or actually formed there.

The initial work of Aschheim and Zondek in 1927, demonstrating that large amounts of gonadotropins were present in the urine of pregnant women, directed attention to the placenta as the most likely extraovarian source. Prior to the in vitro tissue culture studies of hormone secretion by human placental cells, the evidence for the placenta as a secretory organ was based on indirect data. The evidence is voluminous and convincing, yet positive proof was lacking.

Indirect evidence that the placenta is an organ of internal secretion during pregnancy is:

1. Extracts of human placenta implanted into infantile mice and rats produced positive gonadotropic responses. When implanted into castrated mice and rats estrogenic responses resulted.
2. Although the pituitary is enlarged during pregnancy, implants of pituitary into infantile mice failed to show any increase in gonadotropin potency as would be expected if it were the source of the large amounts present in pregnancy.
3. Large amounts of gonadotropin are found in the blood and urine of pregnant patients at the time the trophoblast implants in the uterine bed.
4. Removal of the ovaries as early as the thirty-fourth day of human pregnancy fails to interrupt pregnancy and gonadotropin and estrogens are excreted in the urine.
5. When pregnancy terminates there is a rapid elimination of these hormones with postpartum amenorrhea and atrophy of the genital system.
6. Removal of the fetus in cases of abdominal pregnancy fails to cause significant alteration of the hormone levels until the placenta has been removed or has been absorbed.
7. Association of large quantities of gonadotropin in cases of chorionepithelioma strongly favors the Langhans cell as the productive structure.
8. Histochemical studies of the placenta show presence of large quantities of lipoid substances interpreted as steroid hormones with suggestive data regarding the secretory activity of the Langhans cells as the origin of the gonadotropin.

In spite of all this convincing and indirect evidence, the question still remained unanswered whether these hormones were only stored in the placenta or actually produced there. The value of direct evidence in this study by growth of human placental cells with demonstration of their secretory activity is further emphasized.

It is logical to assume that some secretion from the intraocular placental explants is acting on the pituitary of the rabbit which in turn produces the

formation of corpora hemorrhagica and corpora lutea in the ovaries. Our work with Langhans cells in tissue culture in vitro and histologic demonstration of the Langhans cells in the intraocular explants permit the assumption that these cells are producing gonadotropins which in turn directly stimulate the ovaries.

Might not the presence of gonadotropins or related hormones from the intraocular explants stimulate directly or indirectly the production of estrogens from an extraovarian source in castrated rabbits? Such a source might be the adrenal glands. Histological study of the adrenal glands from several of the animals failed to support this assumption. Daily injections of chorionic gonadotropin over several weeks in castrated rabbits failed to produce uterine growth. Histologic presence of the syncytial cells in the implants is significant.

Kido[3] transplanted human placental tissue in the eyes of rabbits and concluded that the Langhans cells produced gonadotropin. He observed the implants only over a period of twelve to eighteen days, and this is not sufficient time to eliminate the possibility of absorption of the gonadotropin present in the tissue at the time of the implantation. My study shows that absorption of gonadotropin present in the decidua of human pregnancy will give a positive gonadotropin response in the ovaries of rabbits, but as the explant continues to grow additional evidence of the decidual tissue as the site of formation of the hormone is lacking. It is believed from this study with growth of the placental cells over a period of four to six months that the placenta is the site of formation of estrogens and gonadotropin. This study, furthermore, supports the histological studies of Baker and Severinghaus[4] that Langhans cells are present in the placenta throughout pregnancy.

It has been postulated that the syncytial cells arise from the Langhans cells. The question logically follows whether a cell secreting gonadotropin changes to a syncytial cell completely different in structure and function. The embryological nature of this fundamental problem is outside the limits of this paper and remains unanswered.

Evidence of the secretion of progesterone by the placenta was inconclusive. The fact that one castrated rabbit showed progestational changes in the uterus is insufficient data from which to form any conclusions. The curves of excretion of estrogens and pregnanediol during pregnancy are parallel to their highest levels in the last month of pregnancy. Is it not possible that the syncytial cells can metabolize steroid compounds so closely related in their chemical structure as the estrogens and progesterone? There is no reason to assume that, in the absence of a specific cell to which the production of progesterone is attributed, it is, therefore, not produced by the placenta. Bloch[5] demonstrated the biologic conversion of cholesterol to pregnanediol in the eighth month of pregnancy in human subjects. It was assumed that the most likely site of conversion was the placenta.

It has been shown experimentally in animals that the ratio of estrogens and progesterone is important in order to demonstrate progestational changes in the uterus. An excess of estrogens can mask the presence of progesterone. This might explain the absence of progestational changes in the uteri of the experimental animals in this study.

Conclusions

1. Intraocular explants of full-term human placenta were grown in the eyes of rabbits over a period of four to six months.

2. Langhans cell growth was demonstrated by histological examination of the tissue explants. The ovarian response in the test animals as characterized by the formation of corpora hemorrhagica and corpora lutea was evidence of biologic activity of the Langhans cells. These cells were present in the human placenta throughout pregnancy.

3. Syncytial cells grew in intraocular explants as shown by histologic study and biologic activity. Estrogenic stimulation of the uterus of castrated rabbits was found. Injection of urine from the rabbits into spayed mice produced a well-developed vaginal mucosa.

4. Gonadotropin and estrogens were present in the decidua of human pregnancy. Evidence of their formation by the decidua was absent.

5. Evidence favoring the secretion of progesterone by human placental tissue was inconclusive. The uterus of only one castrated animal showed progestational changes.

References

1. Stewart, H. I., Jr., Sano, M. E., and Montgomery, T. L.: J. Clin. Endocrinol. 8: 175, 1948.
2. Jones, G. E. S., Gey, G. O., and Gey, M. K.: Bull. Johns Hopkins Hosp. 72: 26, 1943.
3. Kido, I.: Zentralbl. f. Gynäk. 61: 1551, 1937.
4. Baker, B. L., Hook, S. J., and Severinghaus, A. E.: Am. J. Anat. 74: 291, 1944.
5. Bloch, K.: J. Biol. Chem. 157: 661, 1945.

TOLERATION OF A HIGH WATER INTAKE BY PATIENTS WITH HIGH-GRADE MITRAL STENOSIS IN THE LAST TRIMESTER OF PREGNANCY*†

W. W. HURST, M.D.,‡ AND F. L. MCPHAIL, M.D., GREAT FALLS, MONT.

(From the Department of Obstetrics of the Great Falls Clinic and the Metabolic Unit of the Western Foundation for Clinical Research, Montana Deaconess Hospital, Great Falls, Mont.)

A RECENT report[1] describes the dangers of intravenous fluids in pregnant patients with mitral stenosis in the last trimester. In each of the two cases reported, the total volume given did not exceed 2.5 L. in 24 hours. In each instance pulmonary edema was produced even though neither patient had any previous cardiovascular symptoms. In the first instance 54 Gm. of salt were given in about 52 hours, and in the second more than 12 Gm. in 12 hours were included in the intravenous fluid. Considerable confusion still apparently exists in the medical literature as to what constitutes a judicious supply of water alone, or water plus electrolyte. In such patients salt plus water may so greatly increase the extracellular fluid volume as to produce pulmonary edema or acute congestive heart failure. Our observations indicate that plain water, in amounts *as needed* can be given by mouth, or as dextrose solution in distilled water by vein, without embarrassment to a circulation already failing under the combined disadvantage of near-term pregnancy and mitral stenosis.

The combination of marked narrowing of the mitral valve and pregnancy in the last trimester appears to put the heart at a mechanical disadvantage. Thus, when cardiac failure occurred in a large series[2] of consecutive cases of rheumatic heart disease in pregnancy, it developed in the first eight months in 80 per cent of the cases, with the greatest incidence in the seventh and eighth months. Jensen[3] states that the period of greatest embarrassment to the cardiovascular system begins about the twenty-fourth week and reaches a maximum by the thirty-sixth week of pregnancy.

The small number of observations reported here (Table I) were made from 1933 to 1949. They appear significant because the heart disease was severe enough to necessitate hospitalization during the last trimester of pregnancy, the clinical data were adequate, and no patient was included in the list who did not show classical signs of a well-developed and high grade of mitral stenosis. All patients treated in a similar manner during pregnancy with heart failure and valve lesions which did not fulfill these rigid criteria were excluded from this report.

---

*This study was supported in part by grants from the National Heart Institute, United States Public Health Service, and the Life Insurance Medical Research Fund.

†Read at the Eighteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Milwaukee, Wis., Sept. 21, 22, and 23, 1950.

‡Research Fellow of the American Heart Association.

TABLE I. SUMMARY OF DATA

CASE	AGE (YEARS)	PREV. PREG.	VALVE LESION	ABNORMAL CARDIAC MECHANISM	FUNCT. CLASS	HEART FAILURE MONTH	HOSPITAL DAYS	AVERAGE DAILY INTAKE C.C.	LABOR				REMARKS
									ONSET		DURATION DELIVERY		
									WEEK	METHOD	HOURS	METHOD	
1	19	0	M. S.		IV	7	16	2,500	32	Induced	5	Midforceps	Subacute bacterial endocarditis. Died 9 months post partum. Child living.
2	26	1	M. S.		III	7	4	2,700	38			Section	Spontaneous abortion at 2 months the year before. Tolerated 800 c.c. blood by vein 2 days prior to this delivery. Last seen 3 years later; moderately active.
3	26	0	M. S.		IV	4	29	3,500	40	Spontaneous	12	Low forceps	Pulmonary edema at age 14; again at fourth month of pregnancy. Permanent auricular fibrillation 7 years post partum. Activity moderate. Edema controlled.
4	27	5	M. S.	A. F.	IV	7	36*	4,500	38	Induced	29	Spontaneous	Three spontaneous abortions prior to this pregnancy. Hysterotomy, sterilization 6 years later. Edema controlled, sinus rhythm 12 years post partum.
5	20	0	M. S.		II		15	3,000	40	Spontaneous	22	Spontaneous	Admitted with biliary colic and vomiting. Tolerated 26 Gm. NaCl by vein in 5 days as replacement. Cholecystectomy 7 years later.
6	23	0	M. S.	Sinus tachy.	IV	7	7	6,000	36	Induced	9	Spontaneous	Pregnancy 5 years later, complicated by erythema nodosum. Followed by ligation of Fallopian tubes.
7	21	0	M. S. A. I.		III	7	17	3,200	40	Induced	4½	Midforceps	Recurrence of rheumatic fever 4 years post partum.
	31	1	M. S. A. I., A. S.		IV	7	20	5,300	38	Induced	1½	Version and extraction	See text. This pregnancy 10 years after the one above. Hysterectomy two years later. Moderate activity with no edema 3 years post partum.

8	22	2	M. S. A. I.		III	5	5	5,500	40	Spontaneous	10	Spontaneous	Spontaneous abortion 4 years before. Acute rheumatic fever with therapeutic abortion 1 year before and again 3 years after this delivery.
9	31	2	M. S. A. I.	Auricular ectopic beats	IV	7	9	3,600	40	Spontaneous	6	Spontaneous	Cesarean sections elsewhere twice. Infectious mononucleosis and a threatened abortion with this pregnancy. Active 6 years post partum.
10	30	0	M. S.	Transient A. F.	IV	7	26	3,000	40	Spontaneous	22	Midforceps	Auricular fibrillation during respiratory infection 2 months post partum, and auricular fibrillation permanent 2 years post partum. Active 7 years post partum.
11	19	0	M. S.	Transient A. F.	IV	7	14	3,100	39	Induced	39	Low forceps	See text. 14,400 c.c. by vein over 8-day period. Edema controlled, active 8 years post partum.
12	21	0	M. S.	Auricular ectopic beats	IV	6	19	3,800	28			Section	See text. Subacute bacterial endocarditis, autopsy confirmation. 16,000 c.c. by vein over 9-day period.
13	25	1	M. S. A. I.	Transient A. F.	IV	3	10*	3,300	40	Induced	27	Low forceps	Spontaneous abortion 2 years previous. Erythroblastotic fetus this delivery. Mild episode of failure 2 years post partum.
14	31	0	M. S.		III	8	6	3,800	38	Spontaneous	11	Spontaneous	Thirteen-pound weight loss before delivery. Breech. Episode of mild failure 1 year later.
15	22	0	M. S.	Transient A. F.	IV	5	9*	3,800	39	Induced	7	Low forceps	Recurrence rheumatic fever during pregnancy. Rh negative.
	24	1	Same	Transient A. F.	III	5	7	4,600	34	Spontaneous	12	Low forceps	This pregnancy 2 years after the one above. Macerated erythroblastotic fetus.
16	25	2	M. S. A. I., A. S.	Sinus tachy.	IV	6	12	5,800	42	Induced	3	Spontaneous	Two normal deliveries previously, with an episode of failure in between.

*Sum of two observation periods.

Based on these criteria 21 observation periods in 18 near-term pregnancies of 16 patients were analyzed and summarized (Tables II, III, IV). Five of the 16 patients had aortic insufficiency (Table II) in addition to the mitral stenosis and 2 had aortic stenosis. All but one were rated class III or IV[4] as to cardiac function before hospital therapy was begun, and as an indication of the severity of the heart disease, in almost half of the 18 pregnancies heart failure appeared before the seventh month. Two patients were suffering with subacute bacterial endocarditis. One patient was first seen in an attack of pulmonary edema with profuse expectoration of blood-tinged froth. One had permanent auricular fibrillation, one an obstinate auricular tachycardia, and 7 had episodes of transient auricular fibrillation or extrasystoles. All had been digitalized early in pregnancy or were digitalized when first seen.

TABLE II. MARKED MITRAL STENOSIS (ALL), 16; COMBINED WITH AORTIC INSUFFICIENCY IN 5

COMPLICATIONS PRIOR TO THERAPY			
Myocardial failure (all)	16	Auricular fibrillation, fixed	1
Pulmonary edema	1	Auricular fibrillation, transient	6
Endocarditis (subacute bacterial)	2	Paroxysmal auricular tachycardia	1

Labor was spontaneous in 7, induced in 9, and cesarean section was performed in 2. Delivery was spontaneous in 7, and was assisted by low forceps in 5, by midforceps in 3, and an obstetrical emergency made version and extraction necessary in one. Except for this last patient, surgical anesthesia was not used. All patients had very light analgesia, and for analgesia during severe contractions a mixture of 60 per cent nitrous oxide and 40 per cent oxygen was used. One cesarean section was done under local anesthesia and the other under spinal. Local infiltration anesthesia was used for all episiotomies and repairs.

TABLE III. FLUID INTAKE IN THE 21 PERIODS OF OBSERVATION. AVERAGE LENGTH OF PERIODS 12 DAYS (MAXIMUM 30 DAYS)

Total Average Daily Intake:		
Over 3,000 c.c.	in	19 periods
Over 4,000 c.c.	in	8 periods
Over 5,000 c.c.	in	4 periods

The average length of the 21 observation periods before delivery was 12½ days. The average fluid intake was over 3,000 c.c. in 19 periods, more than 4,000 c.c. daily in 8, and from 5,000 to 6,000 c.c. in 4 of these 21 periods (Table III).

TABLE IV. INTRAVENOUS SUPPLEMENTS USED IN 9 OF 21 PERIODS (5 PER CENT DEXTROSE IN WATER; RARELY SODIUM SOLUTIONS)

Amounts:	500 to 3,000 c.c.	in 24 hour
Volumes:	500 to 1,000 c.c.	at a time
Rates:	15 to 22 c.c.	per minute
Examples:	14,500 c.c.	in an 8-day period
	16,000 c.c.	in an 8-day period

In 9 of the periods of observation intravenous fluids were given (chiefly as dextrose in distilled water, not as "normal saline"[1]) when oral intake was impossible or felt to be inadequate. The amounts given by vein in 24 hours ranged from 500 c.c. to 1,000 c.c. at a time, at a rate of 15 to 20 c.c. per minute (Table IV). Isotonic dextrose in distilled water was used except where emesis or duodenal drainage called for replacement of sodium and/or chloride.

Whenever a sodium-containing solution, including blood or plasma, was given, two or three times its volume of plain water, or isotonic dextrose, was given, in order to provide for vaporization loss and for water for the use of the kidneys.

There was one maternal death, that of a patient with subacute bacterial endocarditis who died three days after cesarean section; the premature (30 weeks) child survived only 24 hours. Another patient with subacute bacterial endocarditis died nine months following delivery. The child survived. Both of these patients were treated before penicillin was available.

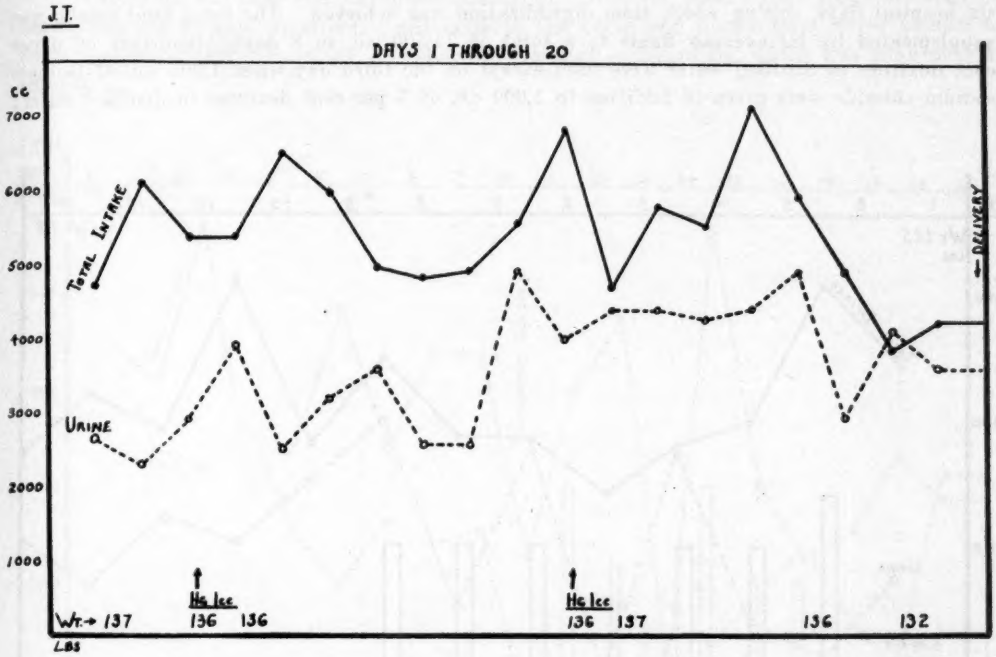


Fig. 1.—Case 7.

There were four infants lost. One, the premature mentioned above, was delivered at 30 weeks. Two were stillborn as a result of erythroblastosis fetalis, and the fourth died from multiple congenital anomalies.

Representative case reports:

CASE 7 (Fig. 1).—J. T., aged 31 years, para i, gravida ii, illustrates the use of a high water intake orally. She had severe rheumatic fever as a child, and a severe recurrence four years before this pregnancy. Her first pregnancy ten years before was managed on a high water intake regimen. She was admitted three weeks before estimated term because of the development of marked dyspnea on exertion, orthopnea, and basal râles, which had persisted in the past month despite digitalization, bed rest, and a low sodium diet at home. The classical findings of mitral stenosis and insufficiency and aortic insufficiency were present. The total oral intake for the twenty days prior to delivery averaged 5,300 c.c. per day, with a maximum in one day of 7,100 c.c. The urine output during the latter part of this period was over 4,000 c.c. per day, and during this time she lost seven pounds of occult edema.

Labor was induced by rupture of the membranes on the twentieth day. A normal cephalic presentation changed spontaneously to a shoulder presentation complicated by a prolapsed hand and cord. Delivery was accomplished by means of a version and extraction with forceps to the aftercoming head.

The patient has been able to care for her two children, with avoidance of heavy work, and with extra rest and attention to her regimen of adequate water and limited sodium diet during the last five years.

CASE 11 (Fig. 2).—R. C., aged 19 years, illustrates the free use of intravenous dextrose in distilled water and minimal but adequate electrolyte replacement after abnormal loss of electrolyte from nausea and vomiting. She had rheumatic fever at age 8, noted shortness of breath and paroxysms of palpitation for two years. She was first seen when 7 months pregnant and after syncope and paroxysmal tachycardia at a ventricular rate of 158 per minute had developed. Basal râles were present, but there was no peripheral edema. The oral intake was quite inadequate and moderate intermittent nausea and vomiting continued during the first six hospital days, during which time digitalization was achieved. The total fluid intake was supplemented by intravenous fluids to a total of 14,500 c.c. in 8 days. Solutions of 5 per cent dextrose in distilled water were used except on the third day when 1,000 c.c. of isotonic sodium chloride were given in addition to 1,000 c.c. of 5 per cent dextrose in distilled water;

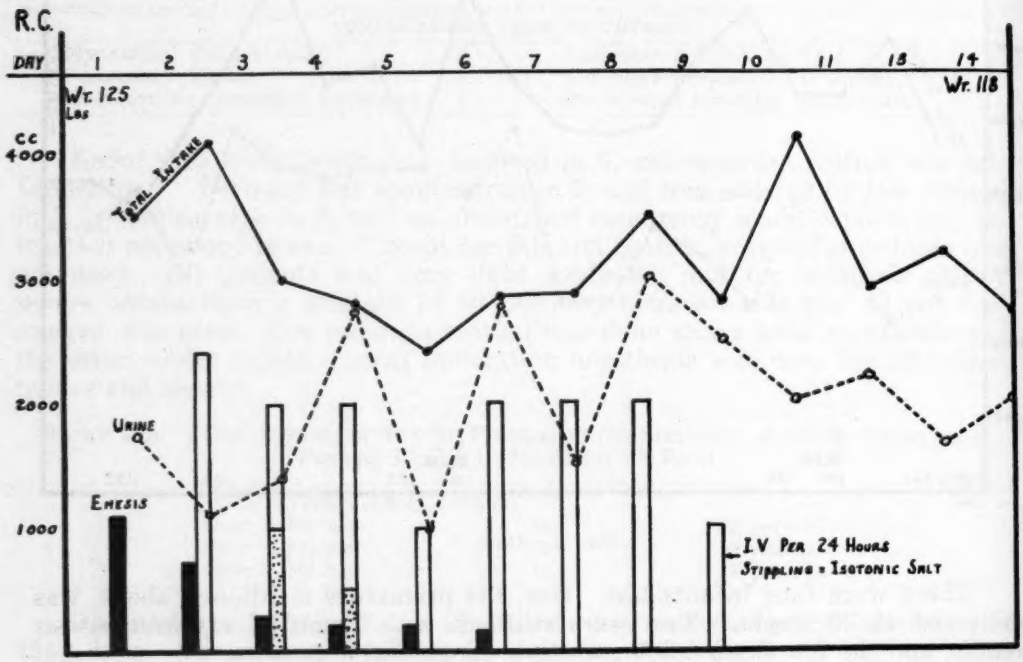


Fig. 2.—Case 11.

and on the fourth day when 500 c.c. of whole blood were given in addition to 1,000 c.c. of 5 per cent dextrose in distilled water. Intake in this period of observation averaged 3,100 c.c. per day with a maximum in one day of 4,100 c.c. Seven pounds of occult edema were lost in this time. Transient cardiac irregularity was noted frequently. Clinically it appeared to be due to auricular fibrillation, although several electrocardiograms failed to catch the irregularity; the duration of the P-R interval was a consistent 0.24 second.

Labor was induced at 38 weeks. Duration of labor was 8 hours. Delivery was aided by low forceps. Nine years later she reported herself as moderately active and quite able to care for her child.

CASE 12 (Fig. 3).—E. C. M., aged 21 years, illustrates removal of gross edema, in the presence of a high water intake supplemented by large amounts of 5 per cent dextrose given intravenously in a patient dying of subacute bacterial endocarditis. In the preceding year she had been told that she had "leakage of the heart." When first seen at six and one-half

months' gestation, she complained of persistent cough and dyspnea, unrelieved by two weeks' rest in bed at home. On admission, cyanosis, dyspnea, and orthopnea were extreme. The face was swollen and there was deep pitting edema of the legs and back. The liver was palpable and profuse râles were present in both lower lung fields. The pulse was regular and the rate 120 per minute. She responded to oxygen, digitalis, ammonium chloride, and 1 c.c. of Mercupurin in 500 c.c. of 5 per cent dextrose in distilled water, given intravenously on the third and seventh days. At the end of the first week a weight loss of eighteen pounds had occurred, and all signs of congestive failure had disappeared except for scattered basal râles. The fluid intake of this period averaged 4,400 c.c. per day.

With a slower rate and improved quality of the heart sounds the typical findings of mitral stenosis became apparent. Red cells in the urine and intermittent fever seemed to justify a presumptive diagnosis of subacute bacterial endocarditis, which was confirmed at autopsy.

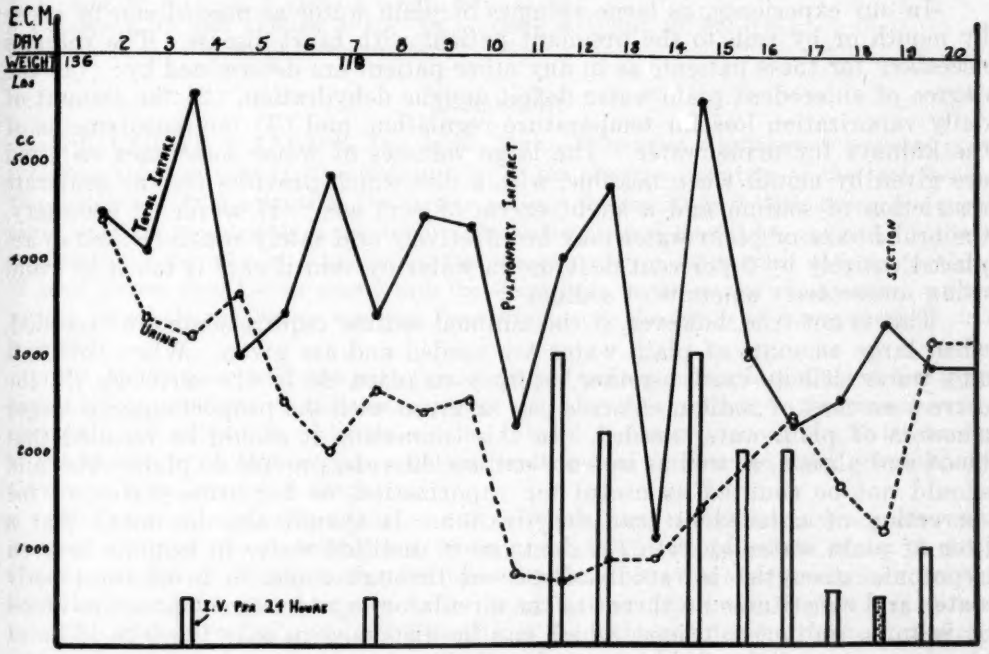


Fig. 3.—Case 12.

From the tenth day, after the initial relief of the congestive failure, and following a pulmonary infarction and other embolic phenomena, her condition deteriorated progressively. A cesarean section was performed on the nineteenth day only in the hope of obtaining a premature child which might survive. Local anesthesia was used. Five hundred cubic centimeters of blood were given during the operation and repeated the following day. Death occurred on the twenty-second day, the third day after section, as a result of another pulmonary embolus and pulmonary edema, at which time she was free of peripheral edema. The 1,060-gram child had survived only 24 hours.

From the time of the first pulmonary infarction the total daily water intake was maintained by intravenous supplements of isotonic dextrose in distilled water in amounts up to 3,000 c.c. per day. From the tenth through the nineteenth day a total of 16,000 c.c. was given, including 1,000 c.c. one and one-half days before death. No intravenous solution was given within 33 hours of the final embolus and a rapidly terminal pulmonary edema.

Comment

When intravenous fluids are necessary to supplement the oral intake or replace electrolyte losses they are chosen carefully from the standpoint of their *composition* as well as volume; they must not carry more sodium chloride than is needed. Without such care concerning the use of sodium-laden solutions, in the presence of a stenosed mitral valve, an elevated diaphragm, and the hydremia of late pregnancy (which should give these patients maximum pulmonary hypertension and vascular engorgement), an increase in extracellular volume is produced and pulmonary edema or acute congestive failure may result.[1] In the cases reported and in pre-eclampsia and eclampsia, where the development of pulmonary edema is always feared, an adequate volume of plain water by vein, as 5 per cent dextrose in distilled water, has failed to produce pulmonary edema and has appeared to be at least in part responsible for recovery and for the clearing of generalized edema.[6, 7, 8, 9]

In our experience, as large volumes of plain water as needed can be given by mouth or by vein to the pregnant patient with heart disease. The volumes necessary for these patients as in any other patient are determined by: (1) the degree of antecedent plain-water deficit or true dehydration, (2) the amount of daily vaporization loss for temperature regulation, and (3) the requirements of the kidneys for urine water. The large volumes of water sometimes required are given by mouth when possible, with a diet which provides for the moderate restriction of sodium and a slight excess of acid ash.[5] However, if necessary, the oral intake of plain water may be effectively and safely supplemented or replaced entirely by 5 per cent dextrose in water by vein if care is taken to avoid using unnecessary amounts of sodium.

This is not true, however, if the minimal sodium requirements are exceeded, when large amounts of plain water are needed and are given. When both salt and water deficits exist together, as they so often do in the seriously ill, the correct amount of sodium chloride can be given with the proportionately larger amounts of plain water needed. In this connection it should be recalled that blood and plasma, as well as isotonic sodium chloride, provide no plain water and should not be counted as useful for vaporization, or for urine water, or for correction of antecedent true dehydration. It should also be noted that a liter of plain water by vein (as dextrose in distilled water in isotonic or even hypotonic strength) is rapidly dispersed through some 50 L. of total body water and constitutes no threat to the circulatory system as compared to blood or isotonic sodium solutions, which can be dispersed in only the 6 to 14 L. of blood or extracellular fluid.

Our observations indicate that as large amounts of water as needed can be given as such by mouth or as dextrose solutions in distilled water by vein, without embarrassment of a circulation already failing under the combined mechanical disadvantages of pregnancy and mitral stenosis. It would appear that true water balance can be safely and beneficially restored or maintained in such patients when proper care is taken to avoid the administration of undue amounts of sodium.

Summary

1. The effects of a high fluid intake on patients with hearts failing under the combined disadvantages of mitral stenosis and late pregnancy, as observed in 21 periods of observation in 18 pregnancies in 16 patients, are reported.

2. Examples are presented of patients receiving large amounts of water by mouth or vein, and of those receiving simultaneously necessary minimal amounts of sodium and/or chloride for replacement of electrolyte losses.

3. It is emphasized that simple administration of "fluids" is not enough. Proper selection of water alone or water plus electrolytes according to the true needs of the individual patient is discussed.

4. The observations suggest that a true water balance can be maintained in such patients without the production of heart failure or pulmonary edema.

References

1. Peters, M., and Penner, S. L.: Am. Heart J. 33: 528, 1947.
2. Gorenberg, H., and McCleary, J.: AM. J. OBST. & GYNEC. 41: 44, 1941.
3. Jensen, J.: Mod. Concepts Cardiovas. Dis. 18: 29, 1949.
4. New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, 1943, Little and Ives.
5. Schemm, F. R.: Ann. Int. Med. 17: 952, 1942; 21: 937, 1944.
6. McPhail, F. L.: J. A. M. A. 111: 1894, 1938.
7. Alvarez, R. R.: AM. J. OBST. & GYNEC. 54: 445, 1947.
8. Chesley, L. C., and Annitto, J. E.: AM. J. OBST. & GYNEC. 45: 961, 1943.
9. Assali, N. S.: Personal communication.

Discussion

DR. GEORGE J. ANDROS, Ann Arbor, Mich.—It becomes a privilege to comment upon a paper which will help to fill a definite void in the obstetric literature of the past decade. The problem of fluid balance in the cardiac patient who manifests failure during late pregnancy warrants considerably more attention from obstetricians than it has received. While it is axiomatic in the rules of good practice that a cardiologist or one familiar with the problems of heart disease should work closely with the obstetrician in the care of the pregnant cardiac patient, we should not divorce ourselves from attention to the details of management of such a patient.

Dr. McPhail has indicated some physiologic and anatomic changes peculiar to late pregnancy which predispose to pulmonary edema and congestive failure in the presence of a stenosed mitral valve. To hydremia and the elevated diaphragm, we might add the burden of weight gain of 10 to 30 pounds, a natural predisposition for salt and water retention, and alterations in the physics of circulation.

The realization by cardiologists some 15 or 20 years ago that patients in congestive failure need not have extreme limitation of fluids has rightfully eliminated the misery of thirst and the discomforts of dehydration for these individuals. On the other hand, there remains a considerable difference of opinion as to the amount of fluid intake a patient in failure should be allowed—or be given. Cardiologists, in the majority of medical centers, prescribe oral fluids as desired by the patient, with no definite maximum or minimum amount designated in advance. Should parenteral intravenous alimentation become necessary, the amount is determined by the particular situation at hand, including climatic conditions and complicating disease. In general, however, the amount of parenteral water would only rarely exceed 2,500 c.c. in 24 hours. It goes without saying that sodium by mouth is limited, and that sodium and chloride by vein are given only for specific calculated replacement, and not always as 0.9 per cent sodium chloride in distilled water or 5 per cent dextrose.

This school of thought feels that improvement in the heart's efficiency, through proper treatment of the decompensation, will result in a mobilization of edema fluid and thereby an adequate amount of water for the kidney as diuresis progresses.

Our essayist's report is illustrative of the "positive hydration" treatment of edema, as first used in cardiac disease by his colleague and co-author, Schemm—and in pre-eclampsia-eclampsia by Dr. McPhail, himself, and later by deAlvarez.

Schemm's concept of hydration for edema stems from the work of Newburgh in nephritis. Newburgh found that the kidney functioned best when supplied with large amounts of water in the presence of a mild systemic acidosis—as produced by the ingestion of an "acid-ash" diet low in sodium, and by the administration of ammonium chloride.

In clinical experiments Schemm has used successfully water alone as a diuretic, withholding digitalis, "acid drugs," and mercurial diuretics when "compatible with the safety of the patient." I should like to ask Dr. McPhail whether or not ammonium chloride was used in the first case? In spite of the tremendous intake, only one pound weight loss occurred in the first two weeks; four pounds in the last six days. Only in the latter period was any significant diuresis taking place—at a time when the patient was in the last week before calculated due date. The membranes were ruptured almost precisely at term date, and almost immediately after delivery the patient was 15 pounds lighter. In the second case presented, urinary output was generally at or below 1,000 c.c. per day (particularly on days 10 through 14) in spite of tremendous intake of fluid. It could be said that the kidneys were putting up one fine struggle. If weight loss did occur, and there was "no peripheral edema" present on admission, where did the weight loss come from?

Perhaps my remarks go beyond the scope of this presentation. Dr. McPhail's primary purpose is to show that large amounts of water have been given to pregnant cardiac patients in failure without catastrophic results. In my mind the basic question involved in a consideration of his report is: "How much water do these cardiac patients and their kidneys require?"

Dr. McPhail speaks of the "large amounts of water as needed," and again, "that true water balance can be safely and beneficially restored or maintained." It would appear to me that water sufficient merely to quench thirst in the oral patient, correct dehydration that is clinically obvious, supply amounts estimated lost through vaporization, sweating, and in the stool, along with any extra quantity needed to carry in electrolytes lost through vomiting, etc., should be considered an adequate amount, providing that diuresis and decrease in weight had been instituted by improvement in the cardiac function and that urine volume was normal. I wonder if this would require as much as 5,000 c.c. by mouth or 3,000 c.c. intravenously in the average patient in whom diuresis is taking place.

Schemm has emphasized the need for extra water to correct dehydration within the cells in such patients, present irrespective of the massive (extracellular) edema. Newburgh states that he has not seen convincing proof of such intracellular dehydration.*

My inference that the possibly excessive water administered is potentially dangerous is made from three standpoints: (a) the possibility of so-called "water intoxication" developing in such patients as may have diseased kidneys and to whom large amounts of fluid are given orally or intravenously at too rapid a rate, (b) the potential hazard of the "low salt" syndrome, and (c) the ever-present threat of pulmonary edema, which would demand even more careful observation of any intravenous infusion than it may be practical to give. The patient's chest must be listened to for râles every fifteen minutes. Other, more simple, observations include the watching for apprehension, increase in pulse rate, deeper and more rapid respirations, greater distention of neck veins, and the tendency on the part of the patient to seek a more upright position.

The pressure of time prohibits a discussion of the possible role played by potassium deficiency in these patients, but a consideration of this aspect may be worthy of another presentation in the future.

DR. McPHAIL (Closing).—The purpose in presenting this paper was twofold: First, in the literature there is considerable confusion between what constitutes "fluid" and what constitutes water. In the article referred to, the fluid was blamed for the resulting complications without comment on the content of the fluid. As shown, there were large amounts of sodium given in both reported cases, and not a great amount of water. The relationship, as suggested by Dr. Andros, between the rather remarkable (at times) weight loss and the less remarkable urine output is important. This phenomenon is the key to the important need of the body for plain water. Water balance data show that in serious illness accompanied by low-grade temperature, hyperventilation, and diaphoresis there is sometimes a remarkable

*Newburgh now regards Eichelberger's study (J. Lab. & Clin. Med. 31: 785, 1946) as convincing evidence of intracellular dehydration in the presence of edema (personal communication to F. R. Schemm, August, 1946).

amount of water lost as vapor, often 2,000 to 3,000 c.c. in 24 hours. If the patient is kept too warm this water loss may be further increased. Thus we may have an important weight loss demonstrated without the necessity of a relative increase in urine output; i.e., loss of weight and of edema without diuresis. This is one of the reasons why we must anticipate, in some patients, a greater intake of water than is sometimes permitted, because there are times when the insensible loss of water is much greater than we realize. "Fluid" containing sodium does not provide water for temperature regulation, only plain water by mouth or dextrose solution in distilled water by vein will do so.

Second, in Montana we have studied our maternal deaths each year. While the number is small, the studies are rather complete. Time and again we find that, either with infection, hemorrhage, toxemia, or with medical complications, such as heart disease, when fluid is given intravenously, it is too often given as a sodium chloride solution. We recognize the need for replacement of sodium and/or potassium deficits. We should also recognize that, when sodium is given either in whole blood, or in plasma or in an intravenous solution, there must be given in addition an adequate amount of plain water to supply sufficient urine water to excrete the urinary solids and to provide for insensible loss.

Finally, we must remember that these are not normal patients. We must remember that their ability to excrete urinary solids is decreased in relation to the cardiovascular-renal damage which may be transient so that later studies may not show the damage. The kidneys are unable, at the time of the illness, satisfactorily to excrete the urinary solids in the smaller amounts of urine water sufficient for entirely normal kidneys. It is therefore important to recognize that in the cases presented there actually was a considerable loss of edema when they were treated as outlined. This means that a true water balance can be safely restored when proper care is taken to avoid the administration of unnecessary sodium either in the diet or in intravenous fluid.

I would like to repeat regarding the first point that a relatively low urine output in the presence of marked loss of weight and of edema often means that the water of vaporization is unusually high, so that relatively large amounts of the water of the edema fluid leave the body by the lungs and skin, while the sodium of the edema fluid is leaving the body in adequate, but nondiuretic, amounts of urine water.

THE SURGICAL MANAGEMENT OF BLEEDING OF LATE PREGNANCY*

ZEPH J. R. HOLLENBECK, M.D., AND JAMES H. WILLIAMS, M.D., COLUMBUS, OHIO

(From the Department of Obstetrics and Gynecology, College of Medicine, The Ohio State University)

THIS study of the surgical management of bleeding in late pregnancy was undertaken primarily to evaluate further cesarean section as a method of delivery of patients with premature separation of the placenta. The incidental inclusion of the cases of placenta previa emphasizes an important danger of error in the differential diagnosis of these conditions. From January, 1939, to July, 1950, in 14,926 deliveries in The Ohio State University Hospital, there were diagnosed and treated by cesarean section sixty-four cases of placenta previa and thirty-six cases of abruptio placentae. These are consecutive on both clinical and private services and were managed by the resident and attending staffs in a ratio of approximately 1.5 to 1. Obviously we have not included any but those cases wherein the diagnosis was made or suspected ante partum.

This series does not include mild cases or those which were suspected as delivery was about to be accomplished, or those diagnosed only on gross examination of the placenta. There was an incidence of severe and moderate abruptio treated by cesarean section of 1 in 415 deliveries. This, as was noted, does not include the mild cases which should be included in any statistical analysis of the incidence of the condition. Irving[1] gives, in his review, an average incidence of 1:248.

Of the 14,926 mothers delivered there were thirty-two deaths, or a rate of 0.214 per cent. Five hundred eighty-nine patients were delivered by cesarean section. This is a general section rate of 3.94 per cent. There were six maternal deaths in the cesarean section group, giving a rate of 1.02 per cent. The 100 cases sectioned because of bleeding of late pregnancy include only one maternal death. This was a case of placenta previa.

Thirty-seven babies (one set of twins) were delivered in the abruptio placentae group of which sixteen were stillborn (43.3 per cent). The neonatal death rate was 18.8 per cent, thus giving a 37.8 per cent fetal survival. Seventy-one and four tenths per cent of the babies who died in the neonatal period were premature. The rate of prematurity in all the infants delivered of mothers with abruptio placentae was 45 per cent. This corresponds with the fact that the average length of gestation in all the cases of abruptio was thirty-six weeks. Despite the fact that many authors (DeNormandie,[2] Falls,[3] Stander,[4] Montgomery,[5] McGlinn and Harer,[6] and Miller[7]) have advocated surgical management of abruptio placentae, Holmes[8] in 1940 and Irving in 1938[1] and again as

*Read at the Eighteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Milwaukee, Wis., Sept. 21, 22, and 23, 1950.

late as 1945[9] consider cesarean section as a dangerous method of delivery compared with the vaginal route. Irving further quotes DeSnoo who gives 6 per cent mortality for vaginal delivery as against 33 per cent for cesarean section.

We quote from an article by J. R. Miller published in 1941 in regard to these authors' reports. "I wish to protest against such use of mortality figures. This is not justified for two reasons: First, no account has been taken of improvement in the matter of transfusions and anesthesia; and second, it is obvious that cesarean sections . . . were done in the more serious type of case. Comparing such operative mortalities with those of the vaginal deliveries, where many cases of minor degree are included, is a fundamental statistical error."

As recently as 1949 McCain and Paliakoff[10] have reported a study of the 293 cases of abruptio placentae at Emory University, Atlanta, Georgia. These cases covered a period of twenty years and represented all degrees of severity of the condition.

In their series the treatment has been rupture of the membranes for induction and spontaneous delivery from below. And, for purposes of study they include only the 224 cases for which they have relatively complete information, clinically. Their cases were "proved" by postpartum inspection of the placenta with findings of separation. Included in the series are 58 mild cases, in which the diagnosis was made *only* on the placental findings and not on the basis of predelivery symptoms.

Infant mortality in their 191 term and premature babies was 60.2 per cent. This figure includes 47 babies from the mild group with a mortality of 27.7 per cent. The maternal mortality was 4.8 per cent of the total 293 cases. This is an 8.5 per cent mortality if we do not include the 58 mild cases and the 69 cases which were not considered otherwise for lack of clinical information. We want to reiterate the protest of Miller in regard to comparison of modern and obsolete methods and further to protest the accentuation of these so-called "conservative methods" in teaching hospitals. This, in our opinion, will only increase the number of patients brought into hospitals in poor condition due to obstetric hemorrhage and therefore cost some of these mothers and infants their lives.

The differential diagnosis of abruptio placentae is not involved from the standpoint of number of simulating disease processes. The differential from the other two causes of most bleeding (with or without pain or pain with or without bleeding) at or near term, is often difficult and not infrequently impossible, roentgenologic diagnostic methods notwithstanding. These other conditions, placenta previa and ruptured uterus, may be every bit as grave as many cases of abruptio. Obviously, uterine rupture is seldom the presenting differential problem whereas placenta previa is. Ruptured abdominal viscus or blood vessel should be mentioned for sake of completeness (Hugenberger, McCord, and Hendricks[11]).

We would like to call attention to our experience in error of diagnosis. In our group of 73 cases diagnosed placenta previa preoperatively, nine were proved to be abruptio placentae. This does not include separation of the low-lying placenta. Here is an error of 12.3 per cent. These findings have influenced us greatly in the management of our cases of placenta previa because, even if this percentage of error is not so great as it would seem here, the inability of the obstetrician properly to evaluate the concealed and increasingly malignant condition of placental separation may lead quickly to the death of the child and may jeopardize the safety of the mother.

Whatever method of management is advocated in abruption all are agreed that prompt emptying of the uterus is imperative as soon after the diagnosis is established as is practicable.

Because the methods of accomplishing this are the subject of controversy, consider the sources of actual or inferred dangers to the mother, a patient with abruptio treated by cesarean section.

1. Hemorrhage.—The volume of blood loss either in internal or external bleeding cannot be accurately estimated or even measured. The separation of the placenta is a progressive condition, the status of which, at any particular moment, cannot be evaluated, nor can its future behavior be prognosticated. Any measure which decreases or stops blood loss is still superior to blood transfusion.

It seems logical then to employ cesarean section because if hemorrhage from the placental site has not been severe it can be prevented and if it has been it can be immediately controlled.

2. Shock.—This is dependent directly or indirectly upon the amount of blood loss, that is to say, by reduction of blood volume and by infiltration of the myometrium. The control of shock, by whatever means, is only temporary in any patient who is still bleeding or can still bleed.

What has been said regarding cesarean section in the prevention of severe hemorrhage is true of shock. It should be emphasized that no patient in shock should be subjected to cesarean section or any other operative or anesthetic procedure until the shock has been treated by blood transfusion and is under control. Time loss at this optimal point of control is to be avoided.

3. Infection.—The danger of infection, including peritonitis and resultant ileus, is markedly reduced with present-day methods of antibiotic and chemotherapy.

Fundamentally as important are the employment of modern surgical methods. We mean by this, among other things, the use of a minimal amount of fine suture material and gentle handling of tissue. By these methods and by the routine use of the lower-segment operation the danger of postoperative intestinal obstruction is obviated.

4. Subsequent Rupture of the Uterus.—This situation can be practically eliminated if the methods referred to are followed and are coupled with the routine delivery of these patients by repeat section before term. There are, of course, some who will deliver previously sectioned patients from below, if these individual patients have certain prerequisites. One dead mother from a ruptured uterus will usually cure this tendency. In our series there were 185 patients operated upon because of previous cesarean section with no maternal mortality.

The obvious danger to the child in abruptio placentae is anoxia and cesarean section seems the quickest way to relieve this real or potential danger. The importance of the prevention of shock in the mother or the prompt treatment of it is necessary for this reason. The use of oxygen in the management of shock is, of course, important to the patient and may be lifesaving to the child.

Summary

A review of 589 cesarean sections, including 100 for bleeding, of which 36 were finally proved to be premature separation, is herewith submitted. This covers an eleven-year period from 1939 to 1950, and includes 14,926 births by all methods.

The method of choice in the treatment of abruptio placentae obviously depends upon the consideration of the dangers to the mother and her infant. The arguments which have been advanced against cesarean section as the treatment for this condition are those of increased maternal mortality and the limitation of subsequent childbearing. These dangers have been lessened by modern surgical technique, anesthesia, and pre- and postoperative care. The time factor

is important to the mother in regard to hemorrhage and shock and to her infant in regard to anoxia. The picture is complicated further by an unavoidable error in the differential diagnosis of abruptio placentae and placenta previa.

In this series of moderate and severe cases the fetal survival rate was 37.8 per cent. In these patients with premature separation of the placenta delivered by cesarean section there were no maternal deaths.

References

1. Irving, F. C.: Internat. Abstr. Surg. 67: 56, 1938.
2. DeNormandie, R. L.: Am. J. Obst. & Gynec. 31: 325, 1936.
3. Falls, F. H.: Journal-Lancet 54: 107, 1934.
4. Stander, H. J.: in Curtis, Arthur Hale: A Textbook of Gynecology, ed. 2, Philadelphia, 1934, W. B. Saunders Company, p. 445.
5. Montgomery, T. L.: Discussion of DeNormandie.[2]
6. McGlinn, J. A., and Harer, W. B.: Am. J. Obst. & Gynec. 30: 226, 1935.
7. Miller, J. R.: Am. J. Obst. & Gynec. 42: 745, 1941.
8. Holmes, R. W.: Am. J. Surg. 48: 61, 1940.
9. Irving, F. C.: Am. J. Obst. & Gynec. 50: 660, 1945.
10. McCain, J. R., and Paliakoff, S. R.: J. A. M. A. 141: 513, 1949.
11. Hugenberber, F. C., McCord, J. M., and Hendricks, C. H.: Ohio State M. J. 46: 789, 1950.

Discussion

DR. ARTHUR B. HUNT, Rochester, Minn.—This is a most provocative paper on the subject of abruptio placentae, a condition which I think most of you will agree is a most dangerous and serious accident in obstetrics, second only to rupture of the uterus.

There seems to be a general trend for the extension and use of cesarean section in nearly all major obstetric complications, whether we individually are sympathetic with it or not; this may herald things to come.

Our material parallels closely that of the authors during the past ten years, in that we had thirty-six cases of moderate to severe abruptio placentae. Our deliveries were only slightly over 10,000, but our cesarean section rate is very close to theirs, 3.5 per cent while theirs is 3.9.

Perhaps it should be noted that this tendency to increase cesarean section in abruptio placentae will not raise materially the incidence in Dr. Hollenbeck's group; it would increase it only about 0.1 per cent. We have achieved almost similar results without the use of cesarean section in abruptio placentae exceeding 25 per cent. Our use of cesarean section in abruptio placentae has doubled in the last two decades, to about 25 per cent.

We feel in reviewing this experience that there are three indications for the use of cesarean section in abruptio placentae. First is the severe case, with progressive abruption of the placenta, where there is still fetal viability; by that I mean the infant looks as though he would weigh over 1,300 grams, and the heart tones are present.

Here the obstetrician has a brilliant chance to justify his specialization by rapid blood replacement and a quick cesarean section effecting fetal salvage in the rather uncommon severe cases.

The second instance wherein we feel there is an indication is an unfavorable condition of the cervix and the uterine dynamics for early, quick delivery from below. Occasionally we have instituted conservative treatment, such as rupture of the membranes, and then had to find that the patient was best treated by cesarean section; but that can be done.

The third instance wherein we feel justified in doing cesarean section in abruptio placentae is when we inspect a Couvelaire infiltrated type of uterus. It should be inspected abdominally to determine whether or not it should be removed in the best interests of the patient.

Our total fetal mortality in our thirty-six cases of severe and moderate abruptio placentae (and I tried very closely to follow Dr. Hollenbeck's selection of these cases, especially in the moderate class) was 57 per cent fetal mortality, comparing almost identically with his figure of 62 per cent.

It should be noted that the two fetal survivals that did occur in the severe cases were by cesarean section. On the other hand, in the moderately severe cases the fetal mortality was 44 per cent for vaginal delivery and 33 per cent for cesarean section delivery.

However, when we exclude those babies that were stillborn, when we first saw the patient with abruptio placentae, and those fetuses that weighed less than 1,300 grams, then our figures for vaginal delivery are better than those for cesarean section as far as fetal mortality is concerned. I think it is harder to justify cesarean section on the basis of fetal salvage in abruptio placentae than it is in placenta previa.

The most important point on which I do not concur with the essayist is the implication that cesarean section should be applied almost routinely. Abruptio placentae is not always a rapidly progressive affair, and its presence usually throws the patient into labor. In many cases the conservative treatment by rupture of the membrane and small doses of Pituitrin gives good results. Each patient presents an individual obstetric condition, and factors such as the cervix and uterine contractions should receive attention.

I do not agree with the argument that cesarean section should be applied for abruption of the placenta because it is good teaching, in that it would provide for the hospitalization of the patient. I think it would be wiser to teach directly that any serious bleeding late in pregnancy needs hospitalization; and then, by a study of the patient, determine whether cesarean section or pelvic delivery seems more advisable.

I should like to say that I certainly do agree with Dr. Hollenbeck and Dr. Williams in that they have just reason to complain about old statistics, because no statistics over fifteen years old, or even ten years old, are now applicable to situations as they exist today.

In the material I have mentioned we have had no deaths from cesarean section, nor any deaths from hemorrhage as far as the maternal mortality is concerned, in this decade.

Since this paper is concerned with the surgical management of bleeding in late pregnancy, a word should be said concerning cases of placenta previa. Our gross mortality was 16 per cent, and we subscribe to the idea that the bag should now be used more sparingly.

For completeness, we would like to mention that in the ten years of this study, and slightly over 10,000 cases, there were ten hysterectomies required for such a situation as rupture of the uterus, uncontrollable postpartum bleeding from fibromyoma or from abruptio placentae, and we feel that these hysterectomies had a good deal to do with coming out of the decade with no maternal mortality.

I would like to concur with the essayists on one point, that effective hemostasis is the main thing in the treatment of hemorrhage late in pregnancy, whether it be applied very rapidly or perhaps slowly but surely. Hemostasis is the thing, and is more vital even than blood replacement in importance, very important as that may be.

DR. DAVID A. BICKEL, South Bend, Ind.—I recently had occasion to review 20,390 deliveries in regard to premature separation. In this number of deliveries there were 102 cases diagnosed as premature separation of the placenta. This group included mild cases, all of which occurred in two general hospitals.

In one of the hospitals 20 per cent of the cases were treated by cesarean section, and in the other 45 per cent of the cases. There were 26 cases which would be considered serious cases, and 76 were mild. The fetal mortality was about the same in both hospitals—25 per cent. This fetal mortality is much less than was reported in the paper, because our figures included mild cases.

I do not think anyone would question the efficacy of cesarean section in the severe cases; but there are many mild cases which, if proper obstetrical judgment is used, do not require section. There was one death in this series of cases—that of a patient who was sectioned, but not soon enough. In the severe cases the factors in management are prompt emptying of the uterus and the administration of blood. Many of the mild cases will deliver safely vaginally, and consequently are not destined to sections in all future pregnancies.

DR. A. W. DIDDLE, Knoxville, Tenn.—Drs. O'Connor, Lambeth, Harry Jenkins, and I recently surveyed the cesarean sections done in a 30-odd-month interval, in Maryville, Oak Ridge, and Knoxville, Tennessee. Among more than 15,000 deliveries there were 766 sections with a varying incidence in the different hospitals of 1.6 to 7.5 per cent. Data were known for 755 women laparotomized. Seventy-three lost their babies before discharge from the hospital. About one-half of the fetal deaths were in cases of section where at least one of the indications for the operation was bleeding. Usually the bleeding was due to premature separation of the normally implanted placenta or placenta previa. Analyzed in another way, about two-fifths of the women sectioned for bleeding lost their babies. Excluding those previously sectioned, it was the feeling that many patients with mild bleeding could have been treated by other means than laparotomy. It was apparent that there should be more careful selection of patients for primary sections with proper evaluation of the fetal salvage.

Three maternal deaths occurred in this series, one was due to uterine rupture. Five other patients survived uterine rupture.

Figures given by the preceding discussants have come from well-controlled clinics. Those we reviewed came from uncontrolled clinics.

DR. RUDOLPH W. HOLMES, Charlottesville, Va.—Early in 1897 I saw my first case of premature separation in the Chicago Lying-in Dispensary, and the second, in consultation in 1899. The former patient recovered, the latter died shortly after her delivery—from exsanguination resulting from hemorrhages for over 24 hours. Immediately after the first instance I began to "read up" on the matter, but results were not good, for the American writings were more than scanty; in 2 years I had investigated over 1,000 volumes and at least double that number of journal articles. Strangely enough the British literature offered extensive reading, really more than all the American and Continental works combined.

In my thesis in those cases which were treated expectantly 15 per cent of the patients died; where more drastic measures were instituted the rate rose to 44 per cent and more: it must be impressed upon you that all cases collected in that thesis were recorded in the last century. In this generation Frederick C. Irving, of Harvard and the Boston Lying-in Hospital, and James H. McCord and his successor, Rudolph Bartholomew, of Emory University have shown that conservative interventions (largely spontaneous)—over 500 cases—bring ideal results. It must be stressed that the prime object is to conserve maternal life as at least 40-50 per cent of infants have died before succor may come.

Arbitrarily, the diverse types may be classified into four divisions of ablatio:

1. Rokitansky retroplacental hemorrhages, of purely pathologic interest. The postpartal inspection of the placenta reveals one or a number of old clots upon its maternal surface; some will be adherent thereon, others will be compressed into depressions in the structure of the afterbirth: if there be a retention for a protracted period the clots will take on a puttylike color due to the disintegration of the hemaglobin: at term the same characteristic will be present in clots retained for a period.

2. Mild cases. The patient rarely will be placed in jeopardy.

3. Severe cases. These are aggravated forms which arouse solicitude on the part of the attendant, will add risk to the patient, and often will demand the exhibition of stimulation and infusions, etc. The internal and external bleeding may be material.

4. The fulminating cases. Fortunately they are infrequent, because of adequate maternal care: indubitably such forms are more infrequent than in prior times: at best, they comprise the tragic episodes of obstetrics. How many have seen such instances: in the extreme cases the woman may be about her wonted task, or resting quietly in bed—suddenly she shrieks that her "uterus is bursting," cries in agony, faints, collapses, has shock, deathly dermal pallor, the uterus enlarges, gross anemia closes the picture in death, with or without a trace of vaginal bleeding, though the unmistakable picture of exsanguination exists.

As regards uterovaginal bleeding: One should never gauge the amount of escaping blood as correlated to the volume retained within the uterus: blood retention is always

primarily due to mechanical damming, then firm clotting. At times, the first evidence of overt blood losses is the escape of pinkish blood serum which may be considerable in amount, and may be confused with escaping liquor amnii.

I present the above graphic picture that it may readily be seen that these diverse degrees of severity do not permit a single line of action. Polypragmatic therapy or intervention in any field of medicine is not appropriate ever. In this strange anomaly of premature separation with such a wide divergence of symptoms and lethality rates, from types merely of pathologic interest to the eventual fulminating type, it would seem proper that we should insist upon a wise discrimination as the keynote of the therapy. We as obstetricians must acclaim that cesarean section is not the panacea for all obstetric ills.

DR. G. KEITH FOLGER, Cleveland, Ohio.—I had the privilege of training for two years in New York, where conservative methods of handling abruptio placentae were practiced. I had the unfortunate experience of watching two mothers die in that hospital during that procedure. I have seen the conservative methods, so-called, of Pituitrin, bags, and so on, and I would like to say that as far as we are concerned abruptio placentae is a surgical case in our hands.

I would like to state that the indications for section in our hands, in late bleeding of pregnancy, are evidence of bleeding or signs in the uterus. We do not quibble whether it is mild, whether it is due to abruptio, or to placenta previa; and yet our section rate is a very respectable figure.

DR. F. J. HOFMEISTER, Milwaukee, Wis.—We work in Milwaukee Hospital which at one time had 75 per cent of the deliveries done by general practitioners. Within the period reviewed (1940-49) that had gradually reversed itself to 25 per cent. One thousand one hundred forty-five of these were cesarean sections. No maternal deaths resulted. Ten maternal deaths occurred during that period of time, but none from bleeding. No maternal deaths resulted from hemorrhage in ten years.

The fetal wastage was only 3.14 per cent: 62 fetal deaths, 28 stillborn, 34 neonatal.

Certainly a record like this speaks for sensible intervention, but not for procrastination.

DR. P. B. RUSSELL, JR., Memphis, Tenn.—We were taught at the Chicago Lying-in Hospital certain fundamental factors. We were instructed, when a pregnant patient has painless bleeding from the uterus, never to make a rectal examination until you have ruled out a placenta previa. The old adage in obstetrics, "painless bleeding" in the last two trimesters of pregnancy is referable to one of two things, is disregarded sometimes, unfortunately. The patient suffers from either some type of placenta previa, or bleeding from some region which has no direct bearing upon the contents of the uterine body.

Abruptio placentae does not occur without some pain being associated and an irritable and tender uterus accompanies this condition. Also, the type of contractions are different, entirely.

The placenta previa type experiences the true contractions of labor, which are accompanied with bleeding to a varying degree. It seems to me, the fault lies with the individual, i.e., a thorough personal history and a careful examination have been neglected. Too many cesarean sections are performed for a low implantation of the placenta and marginal placenta previa. Bag induction has been superseded by the scalpel, it seems.

DR. HOLLENBECK (Closing).—In answer to Dr. Holmes' question, I thought we made it clear in the essay that the cases in which delivery occurred without antepartum signs of separation and in which the diagnosis was based only on the placental findings were not our cases but were the ones with which we were comparing.

Of course, we do not section all of the patients with placentae abruptio. Our percentage actually is 30 per cent, because we obviously do not section the patients who have mild cases; the ones who show evidence of abruption only after delivery, nor the ones who bleed slightly with no other symptoms of embarrassment to the fetus or the mother.

The severe and moderately severe cases, we feel, are the ones in which a cesarean section is necessary for delivery.

In regard to the uterus, there is a general tendency to be conservative and to salvage these uteri if possible. Hysterectomy at time of cesarean section is becoming less common and less frequently indicated.

There are two things that we are apparently not very smart about, because we can't tell how much separation there is going to be, and we can't tell whether or not it is progressive, as has been illustrated in several cases—some of the cases we thought were placenta previas because they were bleeding more than they should. When these patients were sectioned because they were primiparas and the cervix was tightly closed and they were not in labor, and we thought that because the child was viable we could save the life of that child, these "placenta previas" turned out to be abruptios.

Concerning the remarks made about what to do with the general practitioners and others who bring patients to the hospital, and also about getting patients who are bleeding to the hospital, let it be said that actually is the point that we wish to stress today, because conservative methods of management of such cases in the hospitals by the teachers will tend to lead to procrastination by the general practitioner. Our students certainly tend to mimic what we do, and they feel sometimes they can get by with it in the home, whereas they cannot.

THE MALE FACTOR IN STERILITY*

C. O. McCormick, Jr., M.D., Indianapolis, Ind.

ONLY in recent years has the fertility of the husband been given much consideration in the study and treatment of the infertile couple. Even now, study of the husband is often the final procedure in the management of the barren couple, and quite frequently this study is inadequate.

During the past several years, wide experience has shown the husband plays an important part as the cause of a barren marriage. Mazer and Israel[1] state that in at least 40 per cent of sterile unions the husband is either partly or wholly at fault. Michelson[2] in a study of 287 cases of barren marriages found the husband to be a contributing or the sole factor of infertility in 51 per cent of the couples. C. M. McLane[3] recently stated the male to be wholly or partially responsible in 38.2 per cent of barren couples. Lane-Roberts and associates[4] state that male infecundity of varying degree was noted in about 60 per cent of 100 unselected sterile couples. Farris[5] also reports, in 100 unselected sterile couples, the husband was partly or wholly at fault in 60 per cent of the cases.

From these preceding statistics and those of other authorities, it is obvious that the prominent role played by the male in sterile marriages should not be underemphasized. Therefore, not only is it imperative to have an accurate method of semen analysis to determine the potential degree of fertility of the male, but it is also essential to examine the husband's semen early in the procedure of the study of the infertile couple.

As far as the practicing clinician is concerned, it is necessary that he have an easy, accurate method for determining the potential degree of fertility of the husband. The finding of a normal semen indicates normal spermatogenesis, and the presence of active spermatozoa in the cervical canal following coitus (Hühner test) denotes proper deposition of the semen. Thereby, the husband is relieved of any responsibility of the barren marriage in question.

The author wishes to recommend the method of semen analysis as originated by E. J. Farris[5] as an easy, accurate procedure in determining the potential degree of fertility of the male.

His technique is summarized as follows: After five days of freedom from emission or coitus, the husband collects his total ejaculate in a sterile, wide-mouth bottle, having produced it either manually or by coitus interruptus without the use of a condom. The former is the preferable method. In order to allow liquefaction to occur, the specimen is not examined until one to two hours after collection.

Examination consists primarily of computing the number of active sperm in the entire ejaculate, the theory being that only the active sperm are capable

*Read at the Eighteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Milwaukee, Wis., Sept. 21, 22, and 23, 1950.

of reaching and fertilizing the ovum. This counting is carried out in the following manner: A few drops of the well-mixed semen are diluted 1:20 with Locke's solution in a white blood counting pipette. The moving cells are counted upon a red blood cell counting chamber, using a high power objective. The number of active sperm per cubic centimeter of the specimen is computed. With the volume of the ejaculate known, the total number of active sperm in the entire ejaculate is determined. The resulting figure referred to as absolute motility and expressed in millions of active cells is employed as the measure (index) of the individual's fertility.

A highly fertile male is one who has a total of 185,000,000 or more active sperm; a relatively fertile male, 80,000,000 to 184,000,000; a subfertile male, 1 sperm to 80,000,000; and a sterile male, one whose specimen is totally void of sperm.

The speed or drive of the active sperm is determined with the aid of a stopwatch, which measures the time period required by a sperm to travel across one of the 1/20 millimeter squares.

TABLE I. SEMEN ANALYSIS OF 123 MEN WHO HAD 80 MILLION OR MORE ACTIVE SPERMATOZOA AND 55 MEN WHO HAD LESS THAN 80 MILLION ACTIVE SPERMATOZOA

	ACTIVE SPERMATOZOA IN MILLIONS			
	MORE THAN 80 MILLION		LESS THAN 80 MILLION	
	A	B	C	D
1. No. Men	80	43	45	10
2. No. Analyses	84	51	54	11
3. Volume of ejaculate (c.c.)	4.1 (1.2-10.0)	3.9 (0.8-8.0)	3.3 (0.5-9.0)	2.7 (0.8-5.0)
4. Active and inactive spermatozoa per c.c. (millions)	185.31 (41-399)	86 (38-272)	38.9 (1.6-158)	
5. Active spermatozoa per c.c. (millions)	96.3 (28-277)	42 (17-182)	15.2 (0.4-70)	
6. Active and inactive spermatozoa in total ejaculate (millions)	698.9 (295-1656)	299 (160-755)	115.7 (2.8-621)	
7. Active spermatozoa in total ejaculate absolute motility (millions)	365.468 (188-1,114)	129 (80-184)	39.6 (1.4-184)	
8. Percentage of active spermatozoa (motility)	52 (34-69)	47 (15-72)	39 (14-88)	
9. Speed of spermatozoa (drive-seconds)	1.09 (0.64-3.1)	1.24 (0.81-2.3)	1.59 (0.0-3.7)	
10. Percentage of oval forms	81 (65-91)	76 (60-83)	70 (52-90)	
11. Estimated degree of fertility	Highly fertile	Relatively fertile	Subfertile	Sterile (azoospermatic)

The author's method of semen analysis differs in only one respect from that of Farris. In making the morphology study, instead of using the staining method of B. C. Greenberg and co-workers,[5] the author employs that of Kantor.[6]

During the past two years, the author has personally examined 200 semen specimens of 178 married men using Farris' technique. These husbands' specimens were examined because their wives came to us complaining of at least one year's involuntary sterility.

In Table I, these patients have been arranged according to their degree of potential fertility. Columns A and B include 123 men with an absolute motility

of 80,000,000 or more, the highly fertile ones in Column A and the relatively fertile ones in Column B. The 55 men in Column C and D are subfertile and azoospermatic. Column D represents the latter.

It is noted the average number of active spermatozoa per ejaculate in Columns A and B (Line 7), is, respectively, about nine and three times greater than that of the subfertile group, Column C (Line 7).

As one would expect, all figures decrease as one passes from Column A to Column D.

It is interesting to note the average amount of ejaculate of the sterile male is approximately 33 per cent less than that of the highly fertile male.

In Table II, the minimum standards as well as median values for fertility based on Farris' work are listed. Also listed are the median values in twenty cases of pregnancy of the author's from a study of twenty semen samples contributed by the twenty husbands whose wives conceived during the past two years while the couples were being treated for infertility. These twenty semen samples were examined within at least four months of the time of conception.

TABLE II. STANDARDS FOR INDEX OF FERTILITY IN MEN (BASED ON THE METHOD OF DR. E. J. FARRIS)

MINIMUM STANDARDS FOR FERTILITY	MEDIAN (FARRIS, 200 PREGNANCIES)	MEDIAN (AUTHOR'S, 20 PREGNANCIES)
Volume: 2.5 c.c. up	4 c.c.	3.5 c.c.
Speed: 0.7-1.2 sec.*	1 sec.	1.1 sec.
Morphology: 80% or more oval forms	87%	83%
Motility: 38% active sperm	44%	49%
Active per c.c.: 20 million up	51 million	67 million
Index of fertility is based on the number of active sperm in the entire ejaculate in millions (Absolute Motility).—		
Highly fertile: 185 million up	209 million	339 million
Relative fertile: 80-185 million		
Subfertile: 1-80 million		
Sterile: 0		

*Speed is based on timing of 25 progressive sperm.

Of these twenty husbands whose wives conceived, eleven of the men had semen specimens falling in the category of highly fertile, seven in the relatively fertile, and two in the subfertile. Of the seven relatively fertile men, five were rechecked, four of whom still remained in this category, and one was found to be highly fertile. The two subfertile men were rechecked and their status remained unchanged.

These standards for fertility listed in Table II serve only as a guide for evaluating the fertility of the husband. Just because a man does not measure up to these standards does not mean he cannot procreate, but the chances of developing a fruitful marriage are considerably lessened.

Summary

Using Farris' technique of examining semen specimens for determining the potential degree of the male's fertility, 200 semen analyses were done on 178 husbands in 178 unselected infertile couples.

It was found that 123, or 69 per cent, of these men had an absolute motility of 80,000,000 or more sperm and therefore were potentially fertile; while 55, or 31 per cent, were potentially subfertile.

It was found that 10, or 5.6 per cent, of these males were azoospermatic.

In Table II are listed the median values for male standards of fertility based on 20 cases of pregnancy. This series is much too small to draw any conclusions, but the findings are similar to those of Farris.

The author considers the absolute motility count the most important factor in classifying a man's fertility. However, this fertility is affected by other criteria, which must be taken into account.

The author highly recommends Farris' technique of semen analysis as an accurate and relatively easy method for determining the potential degree of the male's fertility in studying the infertile couple.

References

1. Mazer, C., and Israel, S. L.: Menstrual Disorders and Sterility, New York, 1946, Paul B. Hoeber, Inc.
2. Michelson, L.: Diagnosis and Treatment of Impaired Fertility in the Male, Proceedings of the Third American Congress on Obstetrics & Gynecology, 1948, p. 42.
3. McLane, Charles M.: M. Rec. & Ann. 43: 718, 1949.
4. Lane-Roberts, C., and associates: Sterility and Impaired Fertility, ed. 2, Bristol, England, 1948, p. 12.
5. Farris, E. J.: Human Fertility and Problems of the Male, White Plains, N. Y., 1950, The Author's Press, Inc.
6. Kantor, H. I.: Human Fertil. 13: 14, 1948.

621 Hume Mansur Bldg.

Discussion

DR. FREDERICK A. LLOYD, Chicago, Ill.—The method of semen analysis of Farris which Dr. McCormick has so ably presented is really a very simple procedure, and in my opinion an excellent one. The many complex factors which usually serve to complicate the interpretation of every semen study have here been reduced to very simple terms; and the clinician is given a convenient yardstick with which he may readily estimate the potential fertility of a given individual. There has been some disagreement with certain phases of Farris' work. The concentration of the spermatozoa is certainly an important factor. He has, however, assembled a tremendous mass of carefully collected scientific data, and subjected it to an accurate statistical analysis. The masterstroke in his work is the final simplification of his voluminous data in his clinical method of semen analysis and its interpretation. The method is unquestionably good. Whether the final interpretation is completely accurate will depend upon further control studies, such as this report of Dr. McCormick, by other clinicians on a large material.

I personally have never been entirely happy with my estimation of the motility as determined by the wet smear or hanging drop method because there is such a great variation in different microscopic fields. The dilution of the specimen in Locke's solution, as recommended by Farris, and the estimation of the moving spermatozoa on the counting chamber, while it gives much lower values (44 per cent in a highly fertile specimen), is, I believe, easier to carry out and gives us more uniform and accurate results.

The studies on sperm morphology have also been rather involved and difficult to interpret from a clinical standpoint. The question as to what constitutes an abnormal spermatozoon has been very confusing. The concept of the oval form which has been stressed by Hotchkiss and Farris has done much to simplify this problem.

From a study of approximately 400 men who were sent to me for investigation because of a fertility problem I have arrived at a few rather firm practical convictions. Both in the diagnosis and in the treatment one should strive for simplicity. Involved and detailed studies, while important from a research standpoint, are unnecessary in clinical practice. They give little useful information and they are often too expensive for the average young couple who are seeking aid. The examination should include a detailed history and physical

examination as well as a careful evaluation of the genitals. Routine medical laboratory studies are indicated. A basal metabolism test is especially important. The entire examination, including two semen analyses, each after 5 days' abstinence, can usually be completed in four office visits. The main value of such a study is that it gives the gynecologist, who plays the leading role in the handling of the sterility problem, an estimation of the male partner's potential fertility.

The treatment aims first to improve the sperm picture, if this is possible, and then to make the best possible use of the semen which is available by delivering the spermatozoa either by natural intercourse or by artificial insemination as nearly as possible at the time of ovulation. The latter procedure, which falls in the domain of the gynecologist, offers the greatest promise.

The results of therapeutic measures to improve the sperm count and morphology are often discouraging. Too frequently degenerative changes which are irreversible have occurred in the spermatogenic apparatus, so that the testes are not responsive to any therapeutic attack. In our experience simple therapeutic measures are the most effective. These include improvement of the patient's general health and well-being by hygienic measures, sex rest, and the use of thyroid extract. In a few instances in which the basal metabolism is low, thyroid extract, properly administered and controlled, seems to improve the sperm count. But in many cases it fails utterly.

In the occasional case in which disease of the male genitals is present this should be corrected. Severe prostatitis should certainly be treated, many authorities to the contrary notwithstanding.

Wheat germ oil and hormones are worthless. The injection of gonadotropic hormones, at least in their presently available forms, is of no value and its only virtue is that it provides a lucrative income for the physician.

In closing, I wish to stress that the treatment of sterility is a matter of teamwork between various specialists, and the gynecologist is the captain of the team. The so-called sterility specialist, who considers himself an expert in all these fields, is doing the barren couple a great disservice, and he is frequently laboring only for his own gain.

DR. A. J. WHITEHOUSE, Lexington, Ky.—May I ask the author if he thinks abnormal forms of sperm are not a factor in the etiology and treatment of habitual abortion?

DR. McCORMICK (closing).—In response to Dr. Russell's question about the protozoans, I don't know if it has anything to do with the husband being sterile or not; but if we find these organisms we try to eradicate them.

Answering Dr. Whitehouse's question, we have done several semen analyses on husbands whose wives have given histories of repeated abortions, and we have found a high percentage of abnormal forms. In those individuals we have tried some thyroid and have obtained one or two successful pregnancies; but that may be just a coincidence.

I would like to report on how we use this technique clinically. We know that husbands who are highly fertile can have intercourse once every twenty-four hours, and at the third twenty-four hours their count is still 80 million or more, which makes them potentially fertile. With those husbands we do not have to be quite so accurate in timing relations.

A husband who is relatively fertile, that is, whose initial count after five days' abstinence shows a count between 80 and 185 million, at his second intercourse will fall into the subfertile class with a count below 80 million. If he is in the subfertile class, and if his wife is fertile, his chances of making her pregnant are 2 or 3 per cent. If he is relatively fertile we have to be pretty sure of our timing. If we find a husband who is subfertile, or azoospermatic, on repeat examination we do refer him to a urologist.

OXYGEN STUDIES OF THE ARTERIAL BLOOD IN NEWBORN INFANTS*

JOSEPH WATTS, M.D., HAROLD HENDERSON, M.D., D. H. KAUMP, M.D., AND R. M. DAVIS, PH.D., DETROIT, MICH.

(From the Departments of Obstetrics and Gynecology and of Pathology of Providence Hospital and Wayne University College of Medicine)

OBSERVATIONS regarding fetal respiratory physiology and pathology have supplied us with fundamental information on fetal circulation and respiration.[4, 5, 6, 15, 16, 17] This information has allowed us better to evaluate the effects of labor on the infant and to appreciate certain of the factors which may produce states of apnea, asphyxia, and anoxia in the newborn infant.

Eastman has defined asphyxia neonatorum as the failure of the infant to breathe at birth because of an inadequate oxygen supply, and apnea neonatorum as the failure of the onset of respiration in the usual allotted time after birth. However, continued failure of respiration in either case results in anoxia.

Anoxia in newborn infants is thought to be dependent on the factors of prematurity, the trauma of labor, and the analgesic or anesthetic agents used.[2, 3, 9] Much of the controversy regarding anoxia has concerned this latter factor. While it seems well accepted that use of excessive amounts of analgesic or anesthetic agents will be harmful to the newborn child, especially if prolonged,[1, 10, 11, 12] it is controversial whether their moderate use is harmful. Some authors indicate that analgesic or anesthetic agents in any amount definitely increase the incidence of asphyxia in the newborn[2, 3] while others indicate that moderate use of these agents is not harmful.[1] Henderson, Foster, and Eno have concluded that causes other than analgesic and anesthetic agents were found in over two-thirds of their clinically asphyxiated newborn infants. Their work also indicated that the use of general anesthetics for the mother did decrease the infant respiratory response more than analgesic agents alone. When only partial anesthesia was obtained with light ether or chloroform, however, they found the percentage of asphyxiated infants to be the same as was observed in those infants born after the use of analgesics and local anesthesia on the mothers.

Blood gas levels have been determined in human infants and their anesthetized mothers. The results of these determinations indicate that infant oxygenation is not seriously lowered if the mother is given ether or cloroform anesthesia, but when nitrous oxide-oxygen mixtures are used, there is some degree of anoxia, moderate in the mother, and marked in the infant, which parallels the concentration of the anesthetic gases used.[4, 5, 13, 14] When cyclopropane is used as the anesthetic agent, the maternal blood has a pronounced elevation of both arterial and venous oxygen levels, but in the blood of the newborn there is less oxygen than in those infants born under ether anesthesia.[13, 14] It would appear that the excess oxygen is bound to the maternal red cells and not released across the placental barrier. However, while ether anesthesia for the mother appears to give the most favorable results in the

*Read at the Eighteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Milwaukee, Wis., Sept. 21, 22, and 23, 1950.

infant, we must recall that if the ether anesthetic is maintained for any length of time, a grave apnea is produced,[2, 3] perhaps owing to the increased amounts of ether found in the blood of the newborn.[14]

As pointed out by Lull and Hingson, an adequate supply of oxygen to the intrauterine fetus is dependent on the following physiological factors: there must be an adequate oxygen level of the maternal blood, there must be sufficient relaxation of the uterine musculature to permit placental filling, the placental attachment must be sufficient, circulation through the umbilical cord must be free, and there must be normal maternal blood pressure. Certain of these factors are difficult for the obstetrician to control. However, the factors of analgesics and anesthetics which affect maternal oxygenation and circulation can be controlled.

Others have already established the normal maternal blood gas levels.[4, 5, 13, 14] Accordingly, we have studied only the gas levels in infant arterial blood (umbilical vein) immediately at birth, as an index of oxygenation. Smith has pointed out that there is a wide variation in oxygen levels in the newborn. This is interpreted by Snyder to be due to momentary fluctuations in the transport of oxygen and carbon dioxide influenced by the duration, force, and state of uterine contractility. We believe that average blood oxygen level determinations in the newborn, done in sufficient numbers to equalize this fluctuation, will prove reliable in establishing the effect of various factors on infant oxygen content.

Material

We have determined the oxygen content, oxygen capacity, and oxygen saturation levels on 115 samples of newborn arterial (umbilical vein) blood. The mothers of these newborn infants were separated into the following major groups: those who had a normal delivery under ether anesthetic (25 cases), block anesthetic (53 cases), those in whom a major obstetrical maneuver was performed (27 cases), and a miscellaneous group (10 cases) including those with premature infants and other special cases. The blood was collected by clamping a section of the umbilical cord as soon after birth as possible and removing 10 to 15 c.c. of blood under oil. It was then immediately assayed by Van Slyke's manometric procedure. All determinations were made by one of us (J. W.).

Our first series consisted of 25 normally born infants. The mothers of eight of these infants were delivered after less than one minute of open drop ether had been administered. They were usually multiparous. The mothers of the other 17 infants had ether anesthesia for 5 to 8 minutes, which was sufficient for episiotomy and usually low forceps.

In those infants whose mothers had received ether for less than one minute there was an average arterial oxygen content of 13.6 volume per cent and an average oxygen saturation of 66 per cent. In the second group of 17 infants, the average arterial oxygen content was 13.79 volume per cent and there was an average oxygen saturation of 68 per cent. The small difference in oxygen content between the two groups is statistically insignificant, and, as both are within the normal limits previously established,[4, 5, 13, 14] would indicate that short periods of ether anesthesia in the mothers do not produce serious oxygen deficiencies in the infant. No instance of asphyxia in the newborn was found in either group but apnea was present when ether was used for 5 to 8 minutes. This apnea is, in our opinion, due to transplacental passage of ether.

When block anesthetics were used for the mother we had previously noticed a much better respiratory response, better muscle tone and skin color in the infants as compared to those delivered under general anesthetics. In

order to determine if this was related to fetal oxygenation, a group of 53 normal deliveries under block anesthesia was studied. Forty of the mothers were given spinal anesthetics (with and without complimentary analgesic agents) and 13 were given continuous caudal anesthetics (without analgesic agents). Of the 40 mothers given spinal anesthetics there were 8 with an appreciable fall in blood pressure and 32 whose blood pressure levels remained normal. The spinal anesthetics were usually given in the second stage of labor and consisted of a single injection of short-acting Metycaine (30 mg. in the third lumbar interspace) or long acting Pontocaine-dextrose mixtures, with the sensory level usually extending to the tenth thoracic level. The caudal anesthetics were started when there was 3 to 5 cm. of cervical dilatation in a patient with regular uterine contractions.

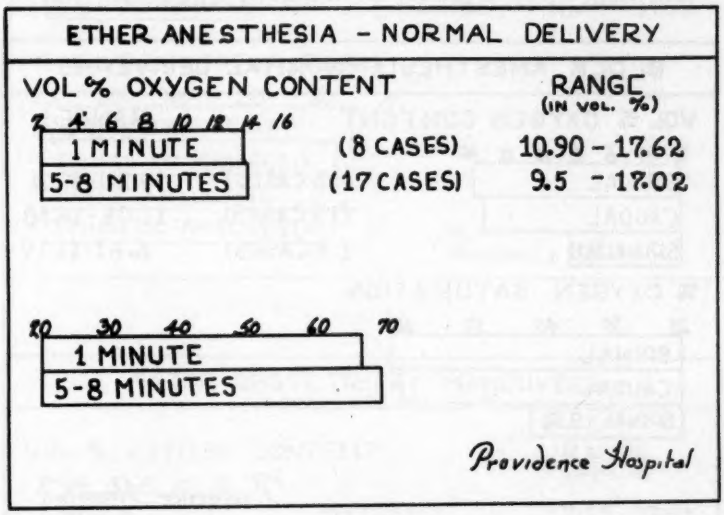


Fig. 1.

The 32 mothers who had spinal anesthetics and sustained normal blood pressure delivered infants with an average arterial oxygen content of 13.99 volume per cent with an average oxygen saturation of 62 per cent. Of the 13 mothers who had caudal anesthetics without analgesic agents, the infants had an average arterial oxygen content of 13.66 volume per cent and oxygen saturation of 60 per cent. The difference in average arterial oxygen content between those infants delivered after caudal or spinal anesthetics is not significant. These oxygen levels compare closely with those obtained in the infants who were born after short ether anesthesia.

From these findings we believe that infants born of mothers under block anesthetics do not have better oxygenation than those born after ether anesthetics but they are not hampered by the depression which occurs with general anesthetic agents.

A fall in blood pressure is a complication occasionally found in patients with spinal anesthetics. In our department slight lowering of the blood pressure is corrected by small amounts of vasopressor agents or elevation of the legs. A more pronounced fall in blood pressure is treated by intravenous vasopressor agents, oxygen inhalation and, rarely, intravenous glucose and saline. The infants born of those mothers with a minimal and easily correctable fall in blood pressure had a normal average arterial oxygen content and

clinically appeared normal. In 8 cases in which there was a drop in maternal blood pressure below 90 to 100 mm. Hg systolic, there was a definite slowing of the fetal heart tones immediately before birth. The blood of these infants had an average arterial oxygen content of 8.46 volume per cent and an average oxygen saturation of 41 per cent. Five of these infants were clinically normal at delivery, but in three there was asphyxia of a degree to require active resuscitation.

The analgesic agents and routine which we follow at Providence Hospital consist of the intramuscular injection during the first stage of labor of Demerol, 100 mg., with scopolamine, 0.7 mg. Depending on the course and activity of labor, some patients receive a second dose of scopolamine and occasionally a second dose of Demerol. Rarely 100 to 200 mg. of Nembutal is added. We feel that these amounts of analgesic agents are not excessive.

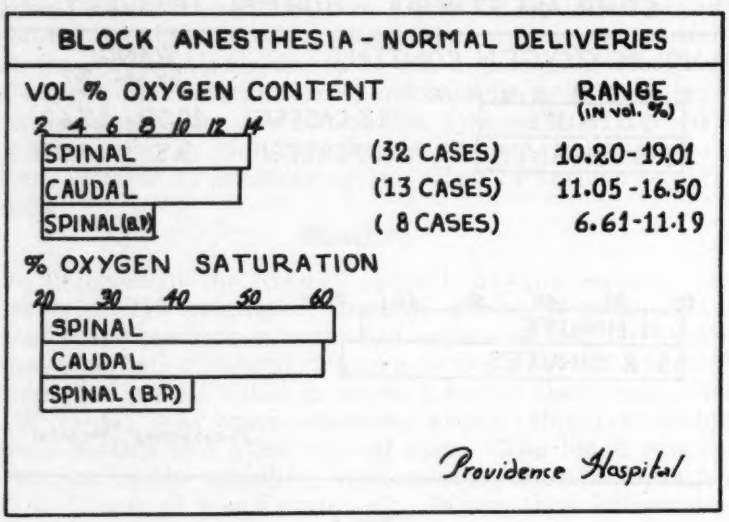


Fig. 2.

In the infants of 23 mothers given spinal anesthetics and the amounts of analgesics listed, there was an average arterial oxygen content of 13.81 volume per cent and an average oxygen saturation of 64 per cent. In this group there was a considerable number of primiparas. In the infants of nine mothers given spinal anesthetics but without complimentary analgesics the average arterial oxygen content was 14.72 volume per cent and the average oxygen saturation 62 per cent. These mothers were usually multiparous, and admitted ready for delivery, with a short second stage.

A similar comparison was made of the infants delivered from mothers under ether anesthesia, both with (20 cases) and without (6 cases) complementary analgesic agents.

In the infants born of mothers under ether anesthesia with analgesics, the average arterial oxygen content was 13.66 volume per cent and the average oxygen saturation 63 per cent. In the infants born of mothers under ether anesthesia but without analgesic agents the average arterial oxygen content was 13.96 volume per cent and the average oxygen capacity 67 per cent. The differences are not statistically significant.

From our study of these patients we believe that analgesics in moderate dosage do not affect fetal oxygenation nor do they significantly increase the incidence of apnea.

Those infants present a special problem who are born following a major obstetrical procedure such as version and extraction, breech delivery, midforceps delivery, and other similar maneuvers. We have studied 27 such infants, 12 delivered under ether anesthesia and 15 under block anesthesia.

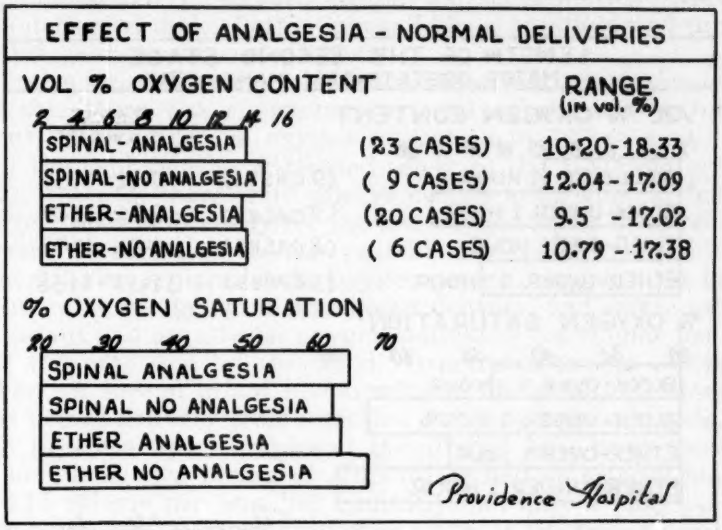

EFFECT OF ANALGESIA - NORMAL DELIVERIES
VOL % OXYGEN CONTENT
RANGE (IN vol. %)
2 4 6 8 10 12 14 16
SPINAL-ANALGESIA (23 CASES) 10·20-18·33
SPINAL-NO ANALGESIA (9 CASES) 12.04-17.09
ETHER-ANALGESIA (20 CASES) 9.5 -17.02
ETHER-NO ANALGESIA (6 CASES) 10.79-17.38
% OXYGEN SATURATION
20 30 40 50 60 70
SPINAL ANALGESIA
SPINAL NO ANALGESIA
ETHER ANALGESIA
ETHER NO ANALGESIA
Providence Hospital

Fig. 3.

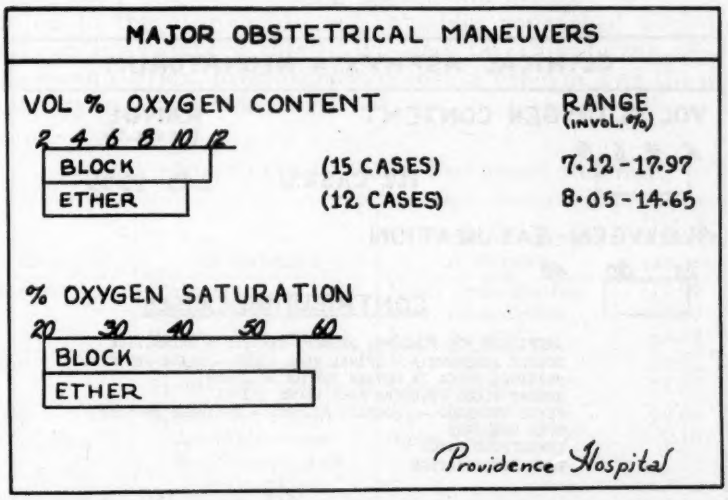


Fig. 4.

In the 12 infants delivered under ether anesthesia the average arterial oxygen content was 10.39 volume per cent and the average oxygen saturation was 58 per cent. In the 15 infants delivered under block anesthesia the average arterial oxygen content was 11.70 volume per cent and the average oxygen saturation was 56 per cent. The oxygen saturation of the infants' arterial blood is significantly reduced as a result of the obstetrical procedures but there is no significant drop attributable to ether as compared to block anesthetics. In this group with the increased trauma of labor and length of the second stage, the factor of depression by prolonged ether anesthesia may add to the possibility of anoxia resulting from apnea.

In addition to the factors of anesthesia and analgesia, and of major obstetrical problems, we must consider the time element introduced by the duration of labor. We have compared the oxygen levels in infants delivered under ether and under block anesthesia when the duration of the second stage of labor is greater and less than one hour.

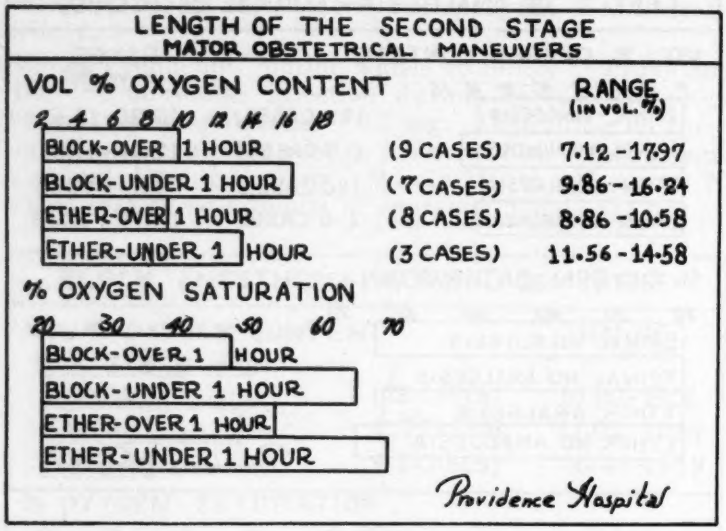

LENGTH OF THE SECOND STAGE
MAJOR OBSTETRICAL MANEUVERS
VOL % OXYGEN CONTENT
RANGE (IN VOL. %)
2 4 6 8 10 12 14 16 18
BLOCK-OVER 1 HOUR (9 CASES) 7.12 - 17.97
BLOCK-UNDER 1 HOUR (7 CASES) 9.86 - 16.24
ETHER-OVER 1 HOUR (8 CASES) 8.86 - 10.58
ETHER-UNDER 1 HOUR (3 CASES) 11.56 - 14.58
% OXYGEN SATURATION
20 30 40 50 60 70
BLOCK-OVER 1 HOUR
BLOCK-UNDER 1 HOUR
ETHER-OVER 1 HOUR
ETHER-UNDER 1 HOUR
Providence Hospital

Fig. 5.

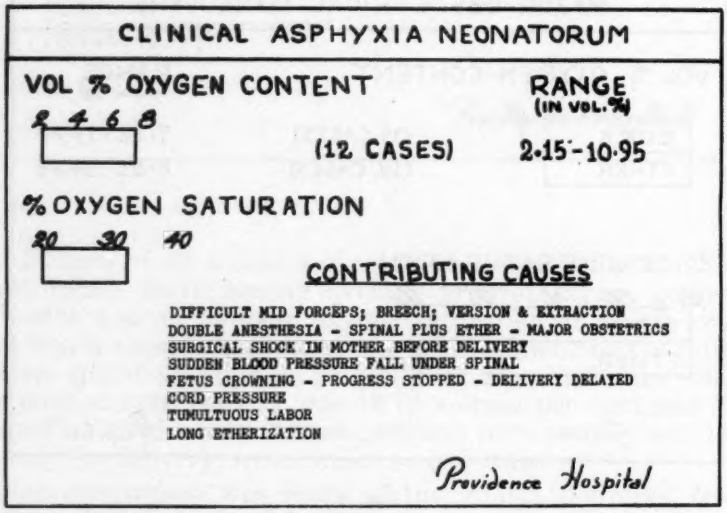

CLINICAL ASPHYXIA NEONATORUM
VOL % OXYGEN CONTENT
RANGE (IN VOL. %)
2 4 6 8
(12 CASES) 2.15 - 10.95
% OXYGEN SATURATION
20 30 40
CONTRIBUTING CAUSES
DIFFICULT MID FORCEPS; BREECH; VERSION & EXTRACTION
DOUBLE ANESTHESIA - SPINAL PLUS ETHER - MAJOR OBSTETRICS
SURGICAL SHOCK IN MOTHER BEFORE DELIVERY
SUDDEN BLOOD PRESSURE FALL UNDER SPINAL
FETUS CROWNING - PROGRESS STOPPED - DELIVERY DELAYED
CORD PRESSURE
TUMULTUOUS LABOR
LONG ETHERIZATION
Providence Hospital

Fig. 6.

There were 3 infants born from mothers with ether anesthetics and with a second stage lasting less than one hour. The average arterial oxygen content was 13.29 volume per cent and the average oxygen saturation was 69 per cent. In the 8 infants born from mothers with ether anesthetics and with a second stage of over one hour the average arterial oxygen content was 9.15 volume per cent and the average oxygen saturation was 53 per cent. In the 7 infants delivered under block anesthesia with a second stage of less than one

hour the average arterial oxygen content was 16.3 volume per cent and the oxygen capacity 65 per cent. In 9 infants delivered under block anesthesia and after a second stage over one hour the average arterial oxygen content was 9.95 volume per cent and the average oxygen saturation was 47 per cent. A definite decrease in arterial oxygen content and saturation is present in newborn infants delivered under both ether and block anesthesia when the length of the second stage increases over one hour.

In our entire series of newborn infants we observed 12 instances of asphyxia. In these infants there was an average arterial oxygen content of 7.24 volume per cent and an average oxygen saturation of 32 per cent. In no instance could the asphyxia be attributed solely to the analgesic or anesthetic agents used. Instead, there were always complicating clinical factors, present in a degree to account easily for the low oxygen levels observed. In these infants a great variation of oxygen content was found and the clinical appearance did not always parallel the oxygen determinations. One infant, born from a mother who was in shock throughout delivery, had severe asphyxia and died. This infant had an arterial oxygen content of 5.4 volume per cent. We believe that this was due to prolonged intrauterine anoxia owing to shock of the mother. A second infant had slowing of the fetal heart tones for several minutes before delivery from a mother under spinal anesthesia. The maternal blood pressure was normal and the altered fetal heart tones were attributed to umbilical cord pressure. This infant had an arterial blood oxygen content of 2.15 volume per cent but clinically had only a mild asphyxia. In two mothers there were spinal anesthetics given at the time of crowning. In both, the fetal head was left on the perineum for 30 minutes. In both infants there was asphyxia with anoxic values in the fetal blood.

In addition to the aforementioned variables concerned with the production of anoxia in the newborn infant, we wish to evaluate the effects of such factors as cesarean section, prematurity, placenta praevia, and the double anesthesia. The study is now in progress.

TABLE I. MISCELLANEOUS CASES, PROVIDENCE HOSPITAL

PROCEDURE	ANESTHESIA	CLINICAL CONDITION OF INFANT	VOL. % ARTERIAL O_2 CONTENT	% O_2 SATURATION
Premature (3 cases)	Drop ether 1-2 min.	Poor, resuscitation	14.04	73
	Spinal, B.P. good	Fair, stimulation	7.86	48
	Spinal, B.P. good	Very good	10.82	51
Cesarean section (2 cases)	Spinal with oxygen	Very good	17.91	68
	Spinal with oxygen	Very good	14.52	67
Twins (one set)	Spinal, B.P. good	Very good	10.58	60
	A—Midforceps	Very good	9.15	55
	B—Version and extraction			
Premature separation placenta (one case)	Drop ether 5 min.	Good	8.61	49
Double anesthesia for version and extraction (2 cases)	Spinal plus ether 10-15 min.	Poor, resuscitation	8.07	39
	Spinal plus ether 20 min.	Very poor, resuscitation	6.64	37

To date we have found no evidence of low oxygen content in two infants born by cesarean section under spinal anesthesia with continuous oxygen inhalation. Of three premature infants, of essentially normal birth, one had a low blood oxygen level but was easily resuscitated. One infant with a normal blood oxygen level, delivered under ether anesthesia, required active resuscita-

tion. One infant delivered under ether anesthesia with placental separation had a moderate depression of the blood oxygen content but was clinically in good condition. There were two infants delivered by version and extraction under combined spinal and ether anesthesia. Both infants had low blood oxygen content levels and both required active resuscitation. The only set of twins in this series was delivered under spinal anesthesia, the first by midforceps and the second by version and extraction. Both infants had low normal arterial oxygen content levels and both were normal clinically.

Summary and Conclusions

1. The arterial (umbilical vein) oxygen content, oxygen capacity and oxygen saturation have been quantitatively determined in 115 newborn infants in order to evaluate the effects on the infant of various factors in the mother. The factors considered included anesthesia, analgesia, major obstetrical maneuvers, and the duration of the second stage of labor, all of which may be concerned in the production of asphyxia in the newborn.

2. Infant arterial blood oxygen levels are within normal limits in uncomplicated deliveries carried out under open drop ether and under block anesthesia. The apnea present in infants born from mothers with ether anesthetics appears to be due to transplacental passage of ether. The apnea is apparently not harmful to the infant and simple means of stimulation restore respiratory activity.

3. Moderate amounts of analgesic agents used in the mother, as outlined, do not significantly alter infant oxygen levels when combined with either ether or block anesthesia.

4. In the infants delivered after major obstetrical maneuvers there were lowered arterial blood oxygen levels and a higher incidence of clinical asphyxia, especially in those delivered under ether anesthesia. The advantage of block anesthesia in the mother appears to be related to absence in the infant of apnea which is found with ether anesthetics. It should be emphasized that the asphyxia present in these infants is not always apparent clinically.

5. In 12 infants there was evidence of asphyxia. The important maternal factors were: fall in blood pressure, umbilical cord pressure, prolonged second stage of labor, and injudicious use of spinal anesthetics.

References

1. Clifford, Stewart: Am. J. Obst. & Gynec. 39: 388, 1940.
2. Cole, W. C. C., and Kimball, D.: Nebraska M. J. 28: 200, 1943.
3. Cole, W. C. C., Kimball, D., and Daniels, E.: J. A. M. A. 113: 2038, 1939.
4. Eastman, N. J.: Bull. Johns Hopkins Hosp. 47: 221, 1930.
5. Eastman, N. J.: Am. J. Obst. & Gynec. 31: 563, 1936.
6. Goldbloom, A., and Gottlieb, R.: J. Clin. Investigation 9: 139, 1930.
7. Henderson, H., Foster, E. B., and Eno, L. S.: Am. J. Obst. & Gynec. 41: 596, 1941.
8. Lull, Clifford B., and Hingson, Robert A.: Control of Pain in Childbirth, ed. 2, Philadelphia, 1945, J. B. Lippincott Company, pp. 323-326.
9. Lund, C. J.: Am. J. Obst. & Gynec. 41: 934, 1941.
10. Schreiber, F.: J. A. M. A. 111: 1263, 1938.
11. Schreiber, F.: J. Michigan M. Soc. 37: 145, 1938.
12. Schreiber, F.: J. Pediat. 16: 297, 1940.
13. Smith, C. A.: Surg., Gynec. & Obst. 69: 584, 1939.
14. Smith, C. A., and Barker, R. H.: Am. J. Obst. & Gynec. 43: 763, 1942.
15. Snyder, F.: Obstetric Analgesia and Anesthesia, Philadelphia and London, 1949, W. B. Saunders Company, pp. 133-159.

16. Snyder, F. F., and Rosenfeld, M.: Am. J. Physiol. 119: 153, 1937.
17. Windle, W. F.: J. Pediat. 19: 437, 1941.

853 FISHER BUILDING

Discussion

DR. A. W. DIDDLE, Knoxville, Tenn.—Dr. Watts and his co-workers gave us an instructive communication, one that all of us should study. They emphasized the danger to the baby of a fall in the maternal blood pressure during labor regardless of the type of anesthetic used. Rightly they condemned anesthetic procedures to delay completion of the second stage of labor and confirmed to my satisfaction that cyclopropane is not the obstetric inhalation anesthetic of choice.

My experimental observations made to ascertain the effect of analgesia on the fetus in utero are meager, but lend support to those given by the essayists. About ten years ago, during my tenure on Dr. Plass's staff, a study was made on a few pregnant women at term while under the effect of Cyclopal, one of the barbiturates. These women were not in labor. Fetal effects were determined indirectly by counting the fetal heartbeats and double checking by recording the fetal heart tones through a stethophone connected to an electrocardiographic attachment. The instrument was built by Dr. Mengert in cooperation with the Department of Engineering at the University of Iowa. In order to affect the fetal heart rate, it was necessary to give the mother an excessive and unpharmacologic dosage of Cyclopal. Under these circumstances the mother became physically overactive and her respiratory rate became depressed. These changes were attributed to cerebral anoxia. Concurrently the fetal heart rate increased supposedly because of anoxic anoxia. It was apparent that as long as the mother suffered no abnormal depressive reactions there was no change in the fetal heart rate. To the contrary, our essayists present evidence to indicate that an infant might not show evidence of central depression until it became necessary for it to respire actively. The clinical experience in my community tends to uphold this opinion. Pediatricians observed that babies born of mothers who received considerable sedation and an inhalation anesthetic during labor frequently had more trouble maintaining a clear airway and more often required resuscitation than did the infants of those not given heavy sedation and inhalation anesthesia. These babies not uncommonly were more drowsy the first day or two of their lives than were those that were not subjected to heavy analgesia and inhalation anesthesia. These observations are in keeping with the recent studies on the electrical activity in the cerebral cortex of newborn babies. Sedation depresses this activity (Hughes, J. G., Ehermann, B., and Brown, V. A.: Am. J. Dis. Child. 76: 626, 1948).

It would be of interest to know if Dr. Watts and his colleagues found any appreciable difference in the oxygen content of the blood of babies whose mothers received comparable dosages of sedation and similar amounts of inhalation anesthesia during labor. It has been my contention that it was impractical to administer these agents, particularly analgesia, in a routine manner, because the depressive reaction produced may vary among different patients, other factors being equal, but clinically I have not been able to prove that point satisfactorily. Recently Dr. K. A. O'Connor and I made a comparative clinical analysis to ascertain the fetal effect of judicious versus nonjudicious use of analgesic drugs commonly employed and inhalation anesthesia during labor. The study was made in three hospitals taking private patients in the Knoxville and Oak Ridge Area. In one hospital these agents were usually given pharmacologically while in the two other hospitals they were administered largely in a routine manner. Procedures to delay completion of the second stage were seldom employed in the first instance. To the contrary, they were not uncommonly used in the second instance. Under the former regime the stillbirth and neonatal death rate was 32.3 per thousand among 6,569 consecutive births. In contrast, under the latter circumstance, the fetal loss among 6,396 consecutive babies was less than 36 per thousand. As one can see, the difference in fetal salvage among the two series was small. When the fetal loss was correlated with the incidence of prematurity and the number of major operative deliveries in the various hospitals, then the difference became negligible. This experience tends to indicate that lethal results with the use of analgesia and anesthesia are often dependent on other contributory factors.

BILATERAL POLYCYSTIC OVARIES, THE STEIN SYNDROME*

MICHAEL L. LEVENTHAL, M.D., AND MELVIN R. COHEN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Michael Reese Hospital, and the Northwestern University Medical School)

IN 1929, Stein performed his first wedge resection of bilateral polycystic ovaries for amenorrhea. Since then, he and his associates[1-5] have reported on an accumulated group of patients who presented what Stein has termed a definite clinical syndrome. "The characteristics of this syndrome are menstrual irregularity featuring amenorrhea, a history of sterility, masculine type of hirsutism, and, less consistently, retarded breast development and obesity. The ovaries are similarly and simultaneously enlarged, and show typical cystic changes which are irreversible and refractory to hormonal therapy. The development of this condition is not congenital; neither is is inflammatory nor degenerative. It is the result of a definite endocrine disturbance." At the time of Stein's last report in 1949, 76 patients seen in private practice over a period of 20 years were operated on for this condition. The chief complaints were amenorrhea and sterility. Forty-eight were married and 28 single, prior to surgery. Menstrual function was satisfactorily restored in all of the single patients and in 90 per cent of the married group. Forty-one patients in the latter group complained primarily of sterility. Twenty-seven, or 66 per cent, conceived one or more times following surgical treatment.

Ingersoll and McDermott[6] recently reported 21 cases of bilateral polycystic ovaries observed at the Massachusetts General Hospital over a 12-year period. They concluded that "a specific entity, polycystic ovaries with thickened tunica albuginea, exists and is associated with a variable clinical syndrome." Their patients presented a more varied clinical picture than that originally described by Stein and Leventhal. Although amenorrhea or oligomenorrhea was the commonest presenting menstrual disorder (13 out of 21 cases), four patients had menorrhagia, and four gave a history of amenorrhea followed by excessive bleeding. Their results were interpreted as satisfactory in 68 per cent of the patients who received adequate surgery. Before surgery, hormonal therapy was uniformly unsuccessful. Meaker[7] reported on 65 patients operated upon for bilateral polycystic ovaries in 22 years. Sixty-six per cent of the infertile patients in his series conceived, and there was a restoration of normal menstrual function in 77 per cent. Hirsutism was manifest in 31 of his 65 patients. Seigler[8] reported 26 cases in 11 years. Eighteen, or 69 per cent, conceived following surgery. Fourteen of his patients were observed from six months to nine years after operation. There was no recurrence of cysts, and the restored menstrual function remained normal. Hirsutism was a symptom in 12 of the 26 patients.

*Read at the Eighteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Milwaukee, Wis., Sept. 21, 22, and 23, 1950.

Among the cases previously reported there are two which are classical examples of the causal relationship between polycystic enlargement of the ovaries and amenorrhea. Stein and Leventhal reported a 29-year-old nulligravida with secondary amenorrhea and sterility present for eight years. There had been complete failure of response to all types of hormonal therapy. Following resection of typical bilateral polycystic ovaries, menstruation appeared one month later (the first in eight years), and continued monthly thereafter. This patient was observed over a period of fifteen years, during which time she had two pregnancies, the first occurring promptly after the first established menstrual cycle. Leventhal[5] reported a patient, aged 30 years, who complained of amenorrhea of seven years' duration and sterility of five years' duration before surgery. All types of endocrine therapy tried by six different gynecologists failed to restore any cyclic bleeding. Bilateral resection of typical polycystic ovaries was followed in 24 days by the first full menstrual flow in seven years. Menstruation has recurred monthly since (observed over a period of eleven years). This patient has conceived voluntarily twice since surgery. There have been several other reports which have described the relationship of bilateral polycystic ovaries to ovarian dysfunction (Robinson,[9] Bailey,[10] Zondek,[11] Reycraft,[12] Jacobson[13]). The number of patients with ovarian dysfunction who require surgical intervention is small compared to the large group of patients with menstrual irregularities and sterility who can be successfully treated by medical means; or in whom restoration of normal physiology is often spontaneous. It has been the lack of careful study and discriminative selection of cases that has made the surgical treatment of ovarian dysfunctions such a debatable subject.

Pathogenesis

Whereas the physiologic change which transforms a normal follicle into an atretic follicle is well known, the mechanism which comes into play to produce a pathological accumulation of cysts associated with fibrosis is not fully understood. It is generally accepted that the etiology of multiple ovarian cysts is on a hormonal basis, involving pituitary-ovarian dysfunction. Cystic follicles in the ovaries have been produced by injections of anterior pituitary hormone into laboratory animals and women. Functionally, disturbances in the diencephalo-hypophyseal pathways may affect the follicular apparatus via the pituitary gland. In recent years, studies on the ovarian circulation have thrown additional light on the mechanism of formation of ovarian cysts. Reynolds[14] described the spiral nature of the arterioles in the ovary of the rabbit, and declared that the spiraling was necessary for growth accommodation when the ovary is stimulated by gonadotrophic hormones. His work was substantiated by Delson,[15] working with the human ovary. The blood pressure in the terminal arterioles is controlled by spiraling, and the orderly change in pressure follows the normal growth and regression of the follicle. Normally, many follicles begin to mature with each cycle but never rupture. These become atretic, and the ovum and granulosa cells degenerate. Obliteration by cicatrix terminates this physiologic change. However, under certain pathologic conditions, associated with a dysfunction of gonadotrophic control, the atretic follicles are stimulated and become larger than usual. According to Reynolds and Delson, there is a distortion of the spiral arterioles in the region of these cysts and they become straightened or "payed out." The increased pressure in the straightened arteriole and associated capillaries causes a transudation of fluid into the enlarged follicle, and it may become an irreversible cystic growth. A repetition of this process may crowd the cortex

with multiple follicle cysts and produce the typical polycystic ovary. Reynolds produced cysts in the ovaries of rabbits by gonadotrophins, and demonstrated a straightening of the coils in the region of the cysts. Delson, in vascular casts of human cystic ovaries, found an uncoiling or "paying out" of the arteriole spirals in the vicinity of the cysts. Furthermore, the fluid in most follicle cysts consists of a transudate, with the presence of little or no estrogen.

Diagnosis

The diagnosis of the clinical condition characteristic of the syndrome is based upon a history of secondary amenorrhea. In the single girl, this may be the only complaint. In the married woman, sterility is the additional complaint and usually the most compelling reason for seeking medical care. There is nothing unusual about the onset of menstruation. For unexplained reasons, the cycle becomes irregular, manifesting increased or diminished bleeding, and ultimately leading to amenorrhea. General physical examination usually reveals nothing pertient, and there are no stigmas of gross endocrine abnormalities. However, hirsutism is not uncommon, occurring in at least 50 per cent of the cases. The secondary sex characteristics, bodily contour, breasts, and clitoris are frequently normal. Bimanual examination reveals a normal or small uterus and bilateral ovarian enlargements. The ovarian growths are firm, smooth, and nonsensitive. The enlargement follows the normal oval contour of the ovary and is constant. It is readily distinguished from the spherical tender enlargement of the solitary follicle or corpus luteum cyst which is inconstant and may disappear entirely, or alternate from side to side. If the patient is obese or the pelvic inclination marked, the examiner, even though dextrous and experienced, may feel only one ovary or may miss both. In such situations, examination under anesthesia may be necessary, but better still a pneumoroentgenogram of the pelvis gives an objective picture of the pelvic organs which is typical and diagnostic (Fig. 1, Case 7). The basal metabolic rate is usually within normal range, and the empiric use of thyroid extract is not followed by restoration of normal function. Even with low metabolic rates, thyroid extract is not beneficial. The use of estrogen and progesterone may produce withdrawal bleeding, but establishment of recurrent menstruation is rare. Gonadotrophic hormones have not produced menstruation. In patients in whom basal body temperatures were recorded preoperatively, the curves were monophasic. Vaginal smears usually revealed cells of the postmenstrual or estrogenic phase, and multiple endometrial biopsies taken during the period of amenorrhea demonstrated proliferative endometrium. Daily smears failed to show cyclic changes of estrogen-progesteron metabolism. However, the vaginal smear on occasion showed cells of the premenstrual type. In these patients the preoperative pregnandiol determinations were high and microscopic examination of the ovarian tissue removed revealed a high degree of luteinization of the theca or granulosa or both (Case 5).

Pathology

In the previous publications from our clinic the microscopic picture was described from the routine reports of the surgical pathological laboratory. In the present study, serial sections were made from the blocks of ovarian tissue removed in an effort to find some anatomic change which might be pathognomonic or characteristic of the syndrome. Grossly, at operation, the ovaries appear enlarged to a size approaching the size of the uterine fundus. The enlargement is in the form of an interpolar elongation, the ovary appearing tense and oval or "eggshaped." The tunica albuginea is thick, tough,

and pearly white. Sections made by cutting reveal a fibrous-appearing capsule and stroma framing innumerable follicle cysts which contain a clear fluid. Microscopically, the tunica is very thick and fibrous. In some sections this marked thickening seems to push the primordial follicles toward the hilus. The follicles are in various stages of development, but the finding of a cumulus with contained ovum is unusual. The granulosa may be thick and many layered, but most often there is a single layer of granulosa cells or none at all. One of the most significant and consistent findings is a marked hyperplasia of the theca interna cells (Figs. 2, 3, and 4). Not infrequently, luteinization was noted in this hyperplastic layer. Evidence of very rapid growth of the

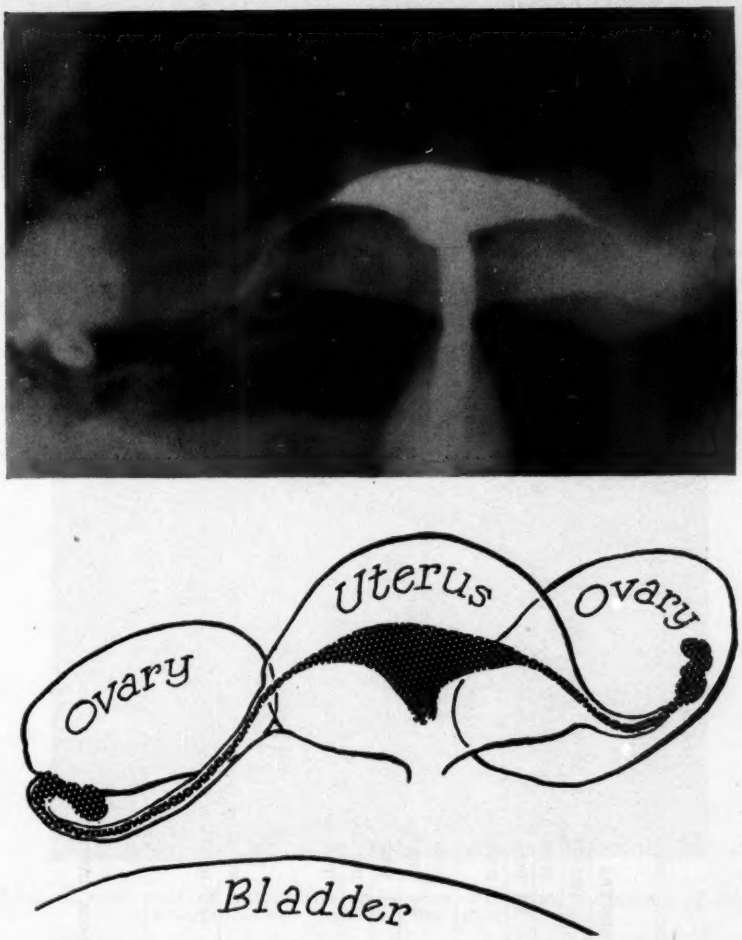


Fig. 1.—Bilateral polycystic ovaries. Combined gynecography.

theca cells was demonstrated by the presence of numerous mitotic figures. In many sections the hyperplastic thecal layer was richly vascularized. The absence of corpora lutea was striking and in only one case of the present series was a corpus luteum found. The marked and persistent hyperplasia of the theca interna with numerous mitoses is a finding not seen in the normal ovary. In summary, the characteristic pathologic findings are (1) follicle cysts, (2) hyperplasia of the theca interna associated not infrequently with lutenization, and (3) fibrosis.

TABLE I. BILATERAL POLYCYSTIC OVARIES. ANALYSIS OF CASES

CASE NO.	MARITAL STATUS	AMENORRHEA		STERILITY	HIRSUTISM	PATHOLOGY*				POSTOPERATIVE RESULTS			PREGNANCY	RECURRENCE
		LONGEST	PRE-OP.			F	F.C.	H.T.	L.	FIRST PERIOD	INTERVAL	HIRSUTISM		
1	M	9 months	5 months	5 years	+	+	+	+	0	42 days	32 days	Improved	+	0
2	M	20 months	20 months	7 years	+	+	+	+	+	36 hours	30 days	Arrested	+	0
3	M	5 months	5 months	0 (contrcp.)	+	+	+	+	0	28 days	30 days	Arrested	+	0
4	M	6 months	3 months	4 years	0	+	+	+	+	36 hours	42 days	0	+	0
5	M	4½ years	4½ years	5 years	+	+	+	+	+	36 hours	28 days	Arrested	0	0
6	M	1 year	1 year	3 years	+	+	+	+	0	72 hours	30 days	Improved	+	0
7	S	9 months	2 months	0	0	+	+	+	0	25 days	28 days	0	0	0
8	S	12 months	4 months	Coitus 7 years (no contraception)	+	+	+	+	+	48 hours	28 days	Improved	+	0
9	S	5 months	5 months	0	0	+	+	+	0	6 days	21 days	0	0	0
10	S	2 years	22 months	0	+	+	+	+	0	5 days	28 days	Improved	+ (post marriage)	+ (1 year post pregnancy)

*F, Fibrosis.
F.C., Follicle cysts.
H.T., Hyperplasia theca interna.
L., Luteinization.

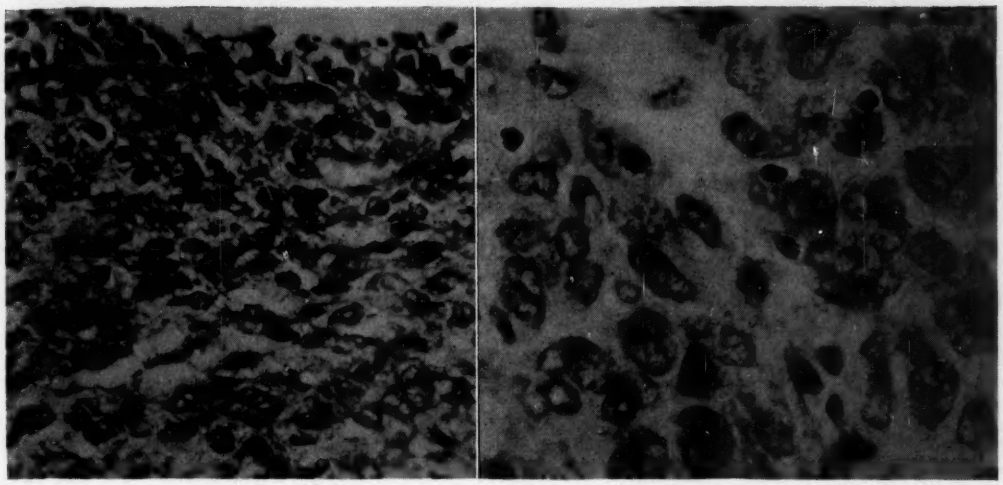


Fig. 2. Fig. 3.

Fig. 2.—Section of cyst wall of polycystic ovary, demonstrating marked hyperplasia of the theca interna layer. (×260.)

Fig. 3.—High-power section of Fig. 2, showing numerous mitotic figures in the theca-interna layer. (×610.)

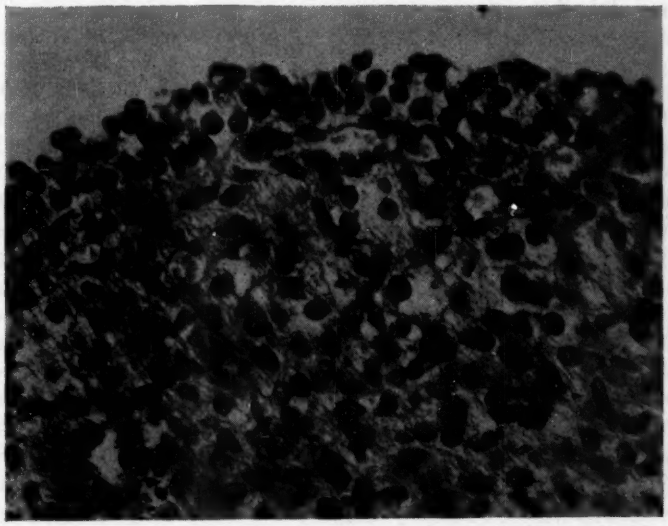


Fig. 4.—Section of cyst wall of polycystic ovary, demonstrating evidences of luteinization in the hyperplastic theca-interna layer. (×300.)

Present Series

The present report is an analysis of 10 cases of bilateral polycystic ovaries with amenorrhea and/or sterility taken from the operating room reports of the gynecologic staff of the Michael Reese Hospital. They were chosen as the only ones acceptable for presentation during the four-year span, 1945-1948. These cases are not included in the reports of Stein. The sparsity in the number of cases (10 in 4 years) again emphasizes the infrequency of the need for surgery in the treatment of certain ovarian dysfunctions. Table I presents an analysis of the 10 cases comprising our present series. In the

married group, the longest duration of amenorrhea varied from 5 months to 4½ years, and in the single group it varied from 5 months to 2 years. In each instance there was a re-establishment of the normal cycle after surgical treatment. There were 5 in the married group who complained of sterility, the duration varying from 3 to 7 years. Four of these became pregnant one or more times, two within one year and two within two years of the operation. One of the single patients became pregnant one year after surgery, whereas no pregnancy occurred during a 7-year period before surgery, during which time intercourse was indulged in frequently without the use of contraceptives. Another of the single patients with periods of amenorrhea up to two years, conceived promptly after marriage. This patient was the only one in the group to have a recurrence. Amenorrhea with polycystic ovaries recurred one year following the birth of her baby.

Hirsutism was present in 7 of the 10 patients. Following surgery, there was an arrest of the hairy growth in 3 and an improvement in 4 of the patients. In no instance did the hirsutism disappear. Hyperplasia of the theca interna layer was a constant finding in the ovarian tissue removed in all the patients. Luteinization of the theca was prominent in 4 patients. In the latter, the first menstruation began within 48 hours following surgery. In two patients (Cases 5 and 8) in whom there was noted marked luteinization of the theca, pregnandiol determinations done before surgery were high.

In order to elaborate further on the chart and to demonstrate the typical syndrome with the results of treatment, the following case reports are presented in more detail.

Case Reports

CASE 1.—Mrs. F. B., aged 26 years, was first seen on Nov. 8, 1946, with a complaint of involuntary sterility and irregular menses associated with long periods of amenorrhea. Her last period was on June 19, 1946 (5 months' amenorrhea). The menarche occurred at age 14. The interval varied from 2 to 8 months, most often 2 to 3 months. Duration of flow was 3 to 8 days with no dysmenorrhea. She was married in 1941 and menstruated regularly for 1 year thereafter. Then the menses occurred every 2 months. In 1944 there was a period of amenorrhea of 9 months' duration. She tried to conceive since marriage (sterility 5 years). The husband's sperm were normal. General physical examination was negative except for hirsutism of the breasts and a male escutcheon. On pelvic examination, the uterus was small and both ovaries enlarged. Pneumoroentgenography revealed a small uterus and both ovaries enlarged, each to the approximate size of the uterus. The following data were obtained prior to surgery: Endometrial biopsy revealed proliferative endometrium on Nov. 22, 1946, and again 2 months later; pregnandiol excretion 1.12 mg. per 24 hours; basal metabolism rate, –18 per cent and –15 per cent. Administration of thyroid extract did not correct the menstrual irregularity. Bilateral ovarian resection was done on March 19, 1947. The pathologic report revealed simple follicle cysts with marked hyperplasia of the theca interna. The first menstrual period postoperatively occurred on April 28, 1947 (42 days postoperatively), lasted 10 days, and was not associated with pain. Subsequent periods occurred on June 21, July 23, Sept. 3, and Oct. 6, 1947. The basal body temperature curve was diphasic, indicating ovulation. On Aug. 22, 1947, quantitative pregnandiol determination revealed 4.5 mg. per 24 hours, indicating a functioning corpus luteum. The patient became pregnant after the October 6 period and delivered a normal infant on July 30, 1948. Repeated bimanual examinations revealed a normal genital status. Following the puerperium, menstruation recurred monthly for 1½ years, after which the patient moved to another city.

CASE 4.—Mrs. G. G., aged 28 years, was first seen on April 15, 1947, complaining of amenorrhea and sterility. Menses began at the age of 13 and had always been irregular, intervals varying from 1 to 6 months, with "spotting." The last regular period occurred on Jan. 5, 1947 (3 months' amenorrhea). The patient had been trying to conceive since

early 1943 (sterility 4 years). Previous investigation included tubal patency tests which were normal and semen examination, also normal. Basal body temperature charts revealed monophasic curves. Previous treatment included cervical dilation and the administration of "shots and pills," without result. Physical examination revealed a well-developed, normal woman. The external genitals were normal and the breasts well developed. The uterus was small and both ovaries were abnormally enlarged. Surgery was done on June 19, 1947, at which time bilateral ovarian resection and curettage were performed. Typical "egg-shaped" ovaries were found. The uterus was small. The pathologic report was "simple follicle cysts with marked hyperplasia of the theca interna; luteinization of granulosa cells; no corpus luteum; hyperplastic endometrium." The patient menstruated in the hospital and irregularly thereafter approximately every 42 days for the next 4 periods. Examination on Oct. 29, 1947, revealed a normal genital status. Records of basal body temperatures were begun with the October period which began on Oct. 16, 1947. The following interpretations were placed upon the probability of ovulation after a close study of the charts:

Cycle Oct. 16 to Dec. 3, 1947—no ovulation.
Cycle Dec. 3 to Jan. 13, 1948—no ovulation.
Cycle Jan. 13 to March 10, 1948—no ovulation.
Cycle March 10 to April 20, 1948—suggestive ovulation.
Cycle April 20 to May 23, 1948—suggestive ovulation.
Cycle May 23 to pregnancy—ovulation and pregnancy.

Delivery was by cesarean section on March 9, 1949. Examination of the ovaries at this time revealed anatomically normal organs. Since delivery, menses have recurred at 5-week intervals. The genital status has remained normal.

CASE 5.—Mrs. R. R., aged 26 years, married 6 years, consulted us on March 23, 1948, complaining of amenorrhea of 4½ years' duration and sterility of 5 years' duration. Galactorrhea had been present for 4 years, but the patient was never pregnant at any time. The menses began at age 14 and were regular every month. Beginning 1½ years after marriage, the interval between periods became progressively longer, at first 2 to 3 months apart, and then 5 to 6 months apart. There had been no menstruation for the last 4½ years. In the past year, withdrawal bleeding was accomplished by the administration of estrogen and progesterone. The patient consulted many gynecologists concerning her sterility and received all types of medication without result. Thyroid extract had been taken for the last 4½ years without effect. The first basal metabolism rate determined 4½ years ago was −28 per cent, and subsequent determinations varied between −10 per cent and +10 per cent. The physical examination was essentially negative except for slight obesity. Pelvic examination revealed a small uterus with bilaterally enlarged ovaries. These findings were confirmed by pneumoroentgenography. X-ray revealed a normal sella tunica. Two determinations of pregnandiol excretion made during this period of amenorrhea were 14.8 mg. per 24 hours and 6.6 mg. per 24 hours. The vaginal smear indicated a persistent premenstrual phase. Surgery was performed on April 15, 1948, when both ovaries were treated by wedge resection. The uterus was small. Suprarenal palpation revealed no enlargements. The pathologic report showed multiple follicle cysts, marked hyperplasia of the theca interna layer with mitoses, with distinct evidence of luteinization, and peripheral fibrosis. The patient bled 36 hours postoperatively and has been menstruating every 28 days since (2 years, 4 months' observation).

CASE 7.—Miss J. A., aged 20 years, consulted us in October, 1946, complaining of long periods of amenorrhea. The menses began at age 13 and were regular every 28 days for the first year, lasting 5 days, with dysmenorrhea. Subsequently, there was a marked irregularity, with periods occurring every 2 to 9 months, the patient menstruating on the average of twice yearly and without pain. She had seen two physicians who treated her with "pills and shots" without results. Physically, the patient was normal and quite thin for her height. The breasts were well developed. Pelvic examination revealed a small uterus, with bilaterally enlarged ovaries. Pneumoroentgenogram showed each ovary enlarged to the size of the uterine corpus. Bilateral ovarian resection was done on Jan. 15, 1947, the last period having occurred on

Oct. 22, 1946. A curettage was done at the same time. The microscopic report showed multiple follicle cysts, with marked hyperplasia of the theca interna and marked fibrosis. The endometrium was in a state of proliferation. The first postoperative period began on Feb. 9, 1947 (25 days postoperatively). Menses have recurred every 28 days since. The patient was last examined in June, 1950, at which time the pelvic status was normal.

CASE 8.—Miss C. D., aged 30 years, consulted us on Jan. 17, 1948, complaining of amenorrhea and generalized hirsutism. The menarche occurred at age 13, lasted 5 days, and recurred thereafter at 3- to 4-month intervals. The periods were not associated with breast engorgement. At age 18-19, the patient did not menstruate for 1 year, after which menses recurred without therapy. For the past two years the menses recurred every 3 to 4 months. The last period was in October, 1947 (3-month amenorrhea). At age 20-22, the pubic and axillary hair became thick, a male escutcheon developed, and hair began to grow on the chest and breasts. In the past 4 years facial hirsutism had developed to the point where the patient was obliged to shave twice monthly. She admitted free indulgence in coitus for the past 7 years without contraception. Pelvic examination revealed normal external genitals. The uterus was small and there was bilateral ovarian enlargement. Pneumoroentgenography on Jan. 23, 1948, confirmed these findings. The sella turcica was normal. Perirenal air insufflation revealed no enlargement of the adrenal glands. Previous to surgery, daily pregnandiol determinations for a period of 7 days revealed an average of 5.3 mg. per twenty-four hours. The determination of 17-ketosteroids at this time revealed 14.5 mg. per twenty-four hours (normal 7-12). These determinations were made after a period of amenorrhea of three months. The basal metabolism rate was plus or minus 0 per cent. An interesting observation was the lack of increase of pregnandiol excretion when 100 mg. of progesterone were given daily, intramuscularly for 3 days. Bilateral ovarian resection was done on Feb. 4, 1948. The pathologic findings were fibrosis, follicle cysts, marked hyperplasia of the theca interna with marked luteinization. The patient bled on the third postoperative day for 48 hours, and has continued to bleed monthly since (observed 2½ years). Since surgery, the hirsutism has diminished on the face but the body hirsutism has remained unchanged. On Sept. 2, 1948, the 17-ketosteroids were 14.9 mg. per 24 hours (last period Aug. 20, 1948). On March 2, 1949, the 17-ketosteroids were 11 mg. per 24 hours (last period Feb. 5, 1949). Endometrial biopsy on Jan. 5, 1949, showed a secretory endometrium (menstruation on Jan. 7, 1949). Although still unmarried, the patient is at present pregnant. The last period occurred on April 26, 1950.

Comment

Ovarian dysfunction, manifested by secondary amenorrhea and associated with polycystic changes in the ovarian cortex, is probably a reflection of dysfunction in the anterior pituitary-ovarian cycle. Whatever the pathogenesis may be, it is a fact that partial resection of the fibrous cortex with its contained cysts is usually followed by the restoration of normal menstrual and reproductive function. The constant demonstration in the cases reviewed in this report of marked hyperplasia of the theca interna layer leads to speculation as to the role this finding may play in the development of the syndrome. Ingersoll and McDermott emphasized the marked increase in size and activity of the cells of the theca interna in some of their cases of polycystic ovaries and remarked about the possibility of hormone production in them.

The production of the ovarian steroids in the cells of the theca interna is well established. In 1938, Corner[16] presented evidence to show that the thecal cells were the principal source of the estrogens. McKay and Robinson[17] in 1941 made histochemical studies on sections of ovary removed at various stages in the menstrual cycle in order to localize the ovarian hormones (which are fat-soluble sterols). They demonstrated reactive material by the use of sudan IV, birefringence, autofluorescence, phenylhydrazine reaction, and sulfuric acid reaction. In every instance, the acetone-soluble substances were found

in the theca interna of the developing follicle, and never in the granulosa layer. They concluded that the theca interna is the site of steroid production. Theca-cell tumors display the histologic characteristics of the theca-interna cells. They have been found to be rich in steroids, the amount depending upon the proportion between the cellular bulk and the fibrous matrix. The majority of the patients with theca-cell tumors reported in the literature are postmenopausal, and bleeding may or may not be a symptom. When the tumor occurs during active menstrual life, amenorrhea is not uncommon. Löffler and Priesel[18] reported a 37-year-old patient in whom the tumor was discovered after a period of amenorrhea of 9 months. Sparling[19] in a report on theca-cell tumors cited the history of a patient, aged 21, who exhibited amenorrhea of 15 months' duration as the principal symptom. After surgical removal of the thecoma, normal menstruation was re-established.

It is probable that a hyperplastic theca layer in polycystic ovaries may produce an excess of steroid which would inhibit true menstruation. Since excessive steroids inhibit follicle stimulating hormone production, one would expect a diminution of secretion of the latter in polycystic ovaries. However, Ingersoll and McDermott report the FSH secretion to be within normal range in 12 patients with polycystic ovaries. Although this finding makes doubtful Stein's original contention that increased anterior pituitary gland secretion accounts for the syndrome, nevertheless it does not rule out the possibility that such a mechanism may be the *original* means of overstimulating the theca.

Hirsutism was manifest in 7 of the 10 patients in our present series, and in over 50 per cent of the patients previously reported. The connection of this finding with thecal hyperplasia has been reported. Culiner and Shippel[20] reported 3 patients in whom hirsutism, amenorrhea, enlargement of the clitoris, and sterility were associated with thecal hyperplasia in enlarged ovaries. Symptoms in all cases regressed after removal of the greater part of the ovarian tissue. They thought that the thecal hyperplasia was productive of androgens. The possibility that the hyperplastic theca may be productive of androgens finds substantiation in experimental evidence. Deanesly[21] transplanted ovaries into the ears of castrated immature male rats, and found that the functional grafts proved to be definitely androgenic as evidenced by their effect on the accessory sex organs. "The androgenic activity seems to be essentially associated with luteinization of the theca interna of the follicles in the grafts." It has been concluded by Deanesly[22] and by Hill [23-24] that the androgen produced was not testosterone. Greene and Burrill[25] have shown that progesterone, in large amounts, is androgenic in the rat and state that "it is conceivable that the androgen produced by the ovaries of these experimental animals may be progesterone." Koets[26] demonstrated an increase in 17-ketosteroid excretion at the approximate time of ovulation in 9 hirsute patients. He proposed that the increase is due to a stimulation of the adrenal cortex by estrogens. Working with animals, he based his conclusions on an increase in the weight of the adrenals at the time of maximum estrogen production (estrus) or by the administration of estrogens. However, this does not necessarily evidence an increased production and liberation of hormones. It is more likely, from the evidence at hand, that the ovary is the seat of androgen production in these patients. In two of the four patients in whom the thecal hyperplasia was associated with luteinization, preoperative pregnandiol excretions were estimated and found to be persistently high. In Case 5, repeated preoperative vaginal smears consistently showed premenstrual cells. These findings indicate progesterone production. Three of the four patients exhibited the most marked degree of hirsutism of the entire group. However, one had no abnormal hairy growth.

It is likely, then, that the symptoms characterizing the syndrome may be due to steroids (estrogen, progesterone, or both) produced in the hyperplastic thecal layer of the follicle in the polycystic ovary. Quantitative variations in the secretion of these steroids may account for abnormalities in the menstrual cycle, most often characterized by amenorrhea. From the foregoing evidence, it is also possible that progesterone or one of its derivatives may exert androgenic effects, including hirsutism.

Summary

1. There is a definite clinical syndrome, associated with bilateral polycystic ovaries, and characterized by menstrual irregularity, featuring amenorrhea and sterility. Hirsutism is a frequent associated finding.

2. The changes in the ovaries are refractory to all present forms of hormonal therapy.

3. Restoration of normal menstrual and reproductive function follows bilateral wedge resection of the polycystic ovaries.

4. Marked hyperplasia of the theca-interna layer is a constant finding in sections of the ovarian tissue removed. Luteinization of this layer is a frequent finding.

5. A working hypothesis for the pathogenesis of this syndrome is presented.

The authors are indebted to Dr. Otto Saphir for his help in the review and interpretation of the microscopic sections, and to Dr. Ronald Greene for his valued suggestions in the preparation of the manuscript.

References

1. Stein, I. F., and Leventhal, M. L.: Am. J. Obst. & Gynec. **29**: 181, 1935.
2. Stein, I. F., and Cohen, M. R.: Am. J. Obst. & Gynec. **38**: 465, 1939.
3. Stein, I. F.: Am. J. Obst. & Gynec. **50**: 385, 1945.
4. Stein, I. F., and Cohen, M. R., and Elson, R.: Am. J. Obst. & Gynec. **58**: 267, 1949.
5. Leventhal, M. L.: Am. J. Obst. & Gynec. **41**: 516, 1941.
6. Ingersoll, F. M., and McDermott, M. V., Jr.: Am. J. Obst. & Gynec. **60**: 117, 1950.
7. Meaker, S. R.: Fertility & Sterility **1**: 293, 1950.
8. Seigler, S. L.: In discussion, Fertility & Sterility **1**: 293, 1950.
9. Robinson, M. R.: Am. J. Obst. & Gynec. **30**: 18, 1935.
10. Bailey, K. V.: J. Obst. & Gynaec. Brit. Emp. **44**: 637, 1937.
11. Zondek, B.: Harefuah **14**: 12, 1938.
12. Reycraft, J. L.: Am. J. Obst. & Gynec. **57**: 1069, 1949.
13. Jacobson, P.: Surg., Gynec. & Obst. **87**: 31, 1948.
14. Reynolds, S. R. M.: Endocrinology **40**: 388, 1947.
15. Delson, B.: Am. J. Obst. & Gynec. **57**: 1120, 1949.
16. Corner, G. W.: Physiol. Rev. **18**: 154, 1938.
17. McKay, D. G., and Robinson, D.: Endocrinology **4**: 378, 1941.
18. Löffler, E., and Priesel, A.: Beitr. z. path. Anat. u. z. allg. Path. **90**: 199, 1932.
19. Sparling, D. W.: Am. J. Obst. & Gynec. **59**: 1279, 1950.
20. Culiner, A., and Shippel, S.: J. Obst. & Gynaec. Brit. Emp. **56**: 439, 1949.
21. Deanesly, R.: J. Physiol. **92**: 2, 1938.
22. Deanesly, R.: Proc. Roy. Soc. s.B **126**: 122, 1938.
23. Hill, R. T.: Endocrinology **21**: 495, 1937.
24. Hill, R. T.: Endocrinology **21**: 633, 1937.
25. Greene, R. R., and Burrill, M. W.: Proc. Soc. Exper. Biol. & Med. **40**: 514, 1939.
26. Koets, P.: J. Clin. Endocrinol. **9**: 795, 1949.

109 North Wabash Avenue

Discussion

DR. EUGENE S. AUER, Denver, Colo.—The paper that Dr. Leventhal has just presented gives added proof that the condition generally known as the Stein-Leventhal syndrome is a clinical entity. There is complete agreement on the clinical picture seen, namely, secondary amenorrhea, sterility, hirsutism, and bilateral ovarian enlargement due to a multiplicity of small cysts filled with a clear fluid.

During the years 1938 through 1948, I have had thirteen typical cases under observation and treatment, ten of which have remained under my care to date. Pain was a more prominent symptom than was mentioned by the authors. Of these ten, seven have become pregnant and six have continued to have fairly regular menstrual cycles. The results from surgery in the remaining three cases were completely nil, the patients remaining amenorrheic and sterile. It is of interest to note that none of these three patients exhibited hirsutism. There was no other essential difference in the gross or microscopic picture between these and the cases successfully operated upon. All presented the large, pearly-white ovaries with extremely thick tunica albuginea, and each one showed hyperplasia of the theca-internal cells, some more marked than others. Corpora lutea, new or old, were *never* found. This was not unexpected, for no woman had a wedge resection less than six months from her last menstrual period. If we accept the theory that the theca interna cells are the source of estrogen production, and there is good evidence for so doing, then the absence of corpora lutea in the presence of a hyperplasia of these cells can be likened to the failure of ovulation and the absence of corpora lutea seen in the ovaries of young women who have been fed large doses of oral estrogens for the treatment of dysmenorrhea.

Perhaps I have seen too few cases. Perhaps enough time has not elapsed. But the fact remains that none of my cases successfully operated upon have become pregnant for the second time. Each became pregnant within six months of their surgery and each was warned that too long an interval should not elapse before getting pregnant again. Neither Stein nor Leventhal has reported a recurrence of the ovarian condition. I believe that it should, and probably *does* occur with greater frequency than has been reported, for whatever may be the cause of these polycystic ovaries simple wedge excision of the ovary should not result in more than temporary relief. Until the cause can be found and eliminated, there is no logical reason to assume that the cystic condition of the ovaries will not recur.

I want to report one case of proved recurrence. The patient, then aged 22 years, was seen in 1944, complaining of having menstruated but seventeen times in the twelve years since the onset of her menses. She had been married four years. She stated that she was extremely frigid and had been unable to conceive. Examination revealed a masculine type of hair distribution plus a right ovary that was at least three times normal size. The left could not be felt. An arrhenoblastoma was suspected. Two months later the left ovary had also become enlarged and the diagnosis of bilateral polycystic ovaries was made and verified at operation. Bilateral ovarian wedges were removed on Oct. 18, 1944. On November 13 the patient stated that her frigidity was gone and she started to menstruate November 18. She had regular periods in December, January, and February. When seen in May, 1945, she was three months pregnant and later delivered a living child. In December of 1948 she was again seen, now complaining of eleven months of amenorrhea and sterility of two years' standing. Examination was essentially the same as it was preoperatively. She remained refractory to all types of medical therapy. Fortunately, she developed acute appendicitis in February of this year and at operation the ovaries were examined and were found to be large and cystic. A wedge was taken from each and thereafter she again became pregnant, her last period being April 20, a fetal heartbeat having been heard last week.

From a purely anatomico-pathologic standpoint, this syndrome is not rare, as the laboratories of our general hospitals will prove. They receive many ovaries characteristic of this syndrome from general surgeons and general practitioners whose limited knowledge of gynecologic pathology makes oophorectomy mandatory when the ovary is enlarged.

I, too, shall add my warning concerning the subjection of any woman to this type of pelvic surgery before a complete study has been made of all the factors that could be re-

sponsible for her sterility and/or amenorrhea. A sufficient time must elapse between the time the diagnosis has been made and surgery done to evaluate the results of empiric thyroid therapy, which should be given in every case in doses of 2 grains daily for several months. In my hands, smaller doses have been ineffective, whereas the use of this large dose has eliminated at least 90 per cent of the cases that I suspected of having the Stein-Leventhal syndrome.

Drs. Leventhal and Cohen should be complimented for keeping this subject up to date and for attempting to arrive at a logical explanation of the pathogenesis of the condition. I believe the operation is of extreme value in the treatment of a certain few carefully selected cases of sterility.

DR. COHEN (Closing).—I want to thank Dr. Auer for adding another series of thirteen patients to our group of those exhibiting the clinical syndrome of amenorrhea, sterility, hirsutism, associated with bilateral ovarian enlargement. His findings were similar to ours. However, our results were dissimilar in that it was quite unusual for our patients to have only one pregnancy.

Dr. Auer has reported one recurrence. Dr. Leventhal also had reported one recurrence in a patient who became pregnant and, following her pregnancy, became amenorrheic and presumably had recurrent bilateral polycystic ovaries. In Dr. Stein's series, there have been no recurrences. We have had the opportunity of performing laparotomies on patients for other conditions and of looking at these resected ovaries several years later, and in no instance were recurrent cysts observed. We feel that this treatment is more permanent than Dr. Auer has indicated. We believe very strongly, however, that patients should be very carefully selected. The fact that a patient is amenorrheic and does not respond to thyroid is no real cause for making her a candidate for ovarian resection unless she really has bilateral polycystic ovaries.

Again I would like to call attention to the fact that in our sections we occasionally see ovulation occurring, or signs of an old ovulation. In other words, it is our belief that, on occasion, patients with polycystic ovaries will ovulate but this ovulation is so rare that it is difficult to predict; hence the patient is clinically sterile.

Rarely one of these patients will become pregnant without surgery. I have a very interesting patient who had all the signs and symptoms of bilateral polycystic ovaries. She was obese, had been amenorrheic for varying periods of time, the typical polycystic ovarian enlargement was demonstrated by pneumoperitoneum, and she had not been able to conceive. Surgery was suggested, but, on examination, I discovered that she was pregnant after an amenorrhea of one years' duration. Her husband was highly fertile, and although she ovulated once in an entire year, timing was excellent and pregnancy occurred. She delivered at term, and three months post partum, when this patient returned because menses had not yet been established, examination revealed that she was again pregnant. She delivered the second baby at term and since then is menstruating normally.

MALIGNANT MYOBLASTOMA VULVAE*

WILLIAM P. SADLER, M.D., MINNEAPOLIS, MINN., AND
MALCOLM B. DOCKERTY, M.D., ROCHESTER, MINN.

(From the Division of Surgical Pathology, Mayo Clinic)

IN 1926 Abrikossoff[1] described a new oncologic entity which he termed "myoblastoma" because of a striking resemblance between its constituent cells and embryonic striated elements, commonly designated as "myoblasts." These tumors occur most frequently in voluntary striated muscle especially of the tongue, but they also occur beneath the skin and mucous membranes where normally there is no voluntary muscle. Appearing as poorly encapsulated, small, solitary, painless lumps usually not exceeding 2.5 to 3 cm. in diameter, their cut surface exhibits a whitish coloration and a firm elastic consistency. Microscopically, they display large granular eosinophilic cells which resemble myoblasts, and a subdivision has been made, based on the presence or absence of uniformity of cell size. Thus "uniform" and "pleomorphic" cell types of myoblastoma are terms in common usage. About 80 per cent are benign and 20 per cent are malignant.

Much literature has accumulated since this rare tumor was established by Abrikossoff[2] and others.[6, 8, 10] In November, 1949, Murphy, Dockerty, and Broders,[13] in a critical analysis of the literature, accepted 219 cases up to October, 1947. They added 10 of their own, in 9 of which the diagnosis was made in the six-year period, 1942 to 1947. In addition, Tonelli[17] reported a series of 21 myoblastomas which had been inadvertently overlooked by several investigators. When we add to this the 52 examples recently recorded by Fust and Custer,[4] the total number of case reports approaches 300.

The tongue appears to be by far the commonest site of involvement (34.1 per cent), with the skin (9.6 per cent), breast (7.9 per cent), subcutis, maxilla, and muscle contributing examples about in the order named.

We were able to find only 4 cases of primary vulvar myoblastoma. In 1937 von Szathmary [14, 15] removed a myoblastoma from the labium minus during a routine vaginal plastic operation. Tamis and Kowles[16] in 1941 removed one from the right labium majus. Their patient had noted the lump three years previously and it had been associated with itching of the overlying skin. The tumor had grown only slightly during this period, and it was excised under local anesthesia. In the third case reported by Murphy, Dockerty, and Broders[13] in 1949, a tumor was discovered during a routine examination of a 72-year-old mulatto woman. It presented as a hard, nontender nodule, 2 cm. in diameter in the right labium majus. Kern, Kaufman, and Combes[6] reported in detail a fourth case in which the lesion simulated granuloma inguinale. None of these 4 vulvar myoblastomas recurred and may be considered benign. We wish to report a fifth case of vulvar myoblastoma.

*Read at the Eighteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Milwaukee, Wis., Sept. 21 to 23, 1950.

Report of a Case

A married white primipara, 40 years of age, presented herself for examination because of a recurrent lump in the left labial region of two months' duration. Her father had died of hypernephroma of the left kidney; her mother is living and suffers from diabetes, but the family history is otherwise negative. Medical history was irrelevant and her present difficulties did not begin until June, 1946, when her local physician in North Dakota removed an "infected sweat gland cyst" from the left labium majus near the clitoris. Unfortunately the material from this procedure was not preserved.

She was first seen by one of us (Sadler) in July, 1947, when she was admitted to Northwestern Hospital, Minneapolis, with the complaint of a recurrent painful lump beneath the scar of the previous operation.

Physical examination revealed a well-nourished, white woman who did not appear to be acutely ill. Positive findings consisted of a cystic endocervicitis and a painful, slightly fluctuant mass beneath the left paraclitoral area in the region of the previous operative scar. No inguinal adenopathy was noted and no other nodules were found elsewhere in the body. Roentgenograms of the chest were "negative." Blood studies did not reveal anemia or leucocytosis. Results of urinalysis were negative as were those of the Kline test for syphilis. The clinical diagnosis was made of infected sebaceous cyst and cystic endocervicitis.

On July 30, 1947, dilatation and curettage were performed with linear cauterization of the cervix. The tender cystic mass was excised. It ruptured during the dissection and appeared to contain infected sebaceous material.

The pathologic report stated that sections of the cyst showed the lining to contain a large amount of granulation tissue, surrounded by fibrous connective tissue. One area contained a small remnant of squamous epithelium which suggested an epidermoid cyst. Evidence of malignancy was not present. A diagnosis was made of infected epidermoid cyst.

Subsequent history showed that in October, 1948, the patient returned with the complaint of a hard, nonpainful lump beneath the site of the scar of the previous operation and a separate lump in the midleft inguinal region. She had noted this recurrence two months previously. Operation was advised and done on Oct. 11, 1948, at Northwestern Hospital, Minneapolis. A left inguinal incision was made extending down to the left paraclitoral region and upper labium. Beneath the site of the previous operation a firm, hard nodule, rubbery in consistency, measuring 3 by 2 cm. was found. It was excised and wide block dissection of the left inguinal region was done. A soft cellular tumor 2 cm. in diameter, and three smaller nodules were removed together with the subcutaneous fat. The postoperative course was uneventful. The wound healed and the patient was discharged on the fifth postoperative day.

This tissue was examined by several competent pathologists who concurred in a diagnosis of sarcoma of the left inguinal region of low grade. The type was not determined. A review of the sections of the cyst removed the previous July and diagnosed as infected epidermoid cyst, showed a few cells similar to the predominant cells of the second tumor. Dr. Emil Novak of Baltimore reviewed the sections on Oct. 1, 1949, and considered the tumor to be a sarcoma. He suggested that it might have taken origin from some of the embryonal vestigial remnants of the Wolffian duct.

The patient returned for re-examination Sept. 14, 1949, stating that she felt well, generally. Examination at this time revealed a nontender pea-sized mass involving the left labium majus about 1.5 cm. below the site of the original tumor and its previous recurrence. Biopsy was advised and urged. She postponed the procedure owing to a "really important" family emergency and was not seen again until Jan. 4, 1950. By this time the nodule noted three months previously had increased in size to about 1.5 cm. in diameter. Operation was advised. The patient expressed a desire to go to the Mayo Clinic and was referred to Dr. V. S. Counseller. At operation on Jan. 30, 1950, the labium was split and all fat from the bottom of the labium up along the clitoris and out on the groin and all glands of the left inguinal region were removed. Her convalescence was uncomplicated and she was discharged on Feb. 11, 1950.

Microscopic Findings

Material from the first operative procedure unfortunately was not available for microscopic study. Material from the first and second recurrences exhibited fibrous and fatty tissue densely infiltrated by manifestly malignant spindle cells which appeared to be growing in irregular sheets and strands (Fig. 1). Under

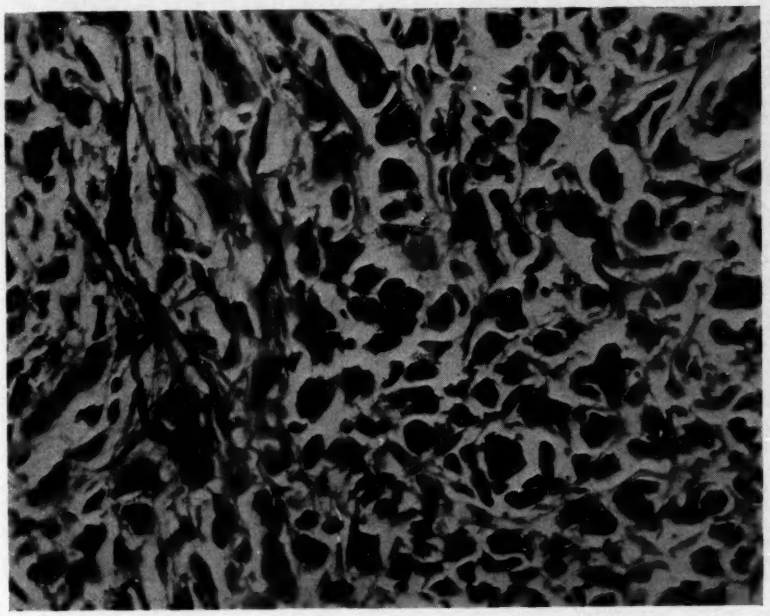


Fig. 1.—Myoblastoma vulvae showing the preponderance of large eosinophilic granular cells which characterized the first recurrence of the lesion (hematoxylin and eosin, ×300).

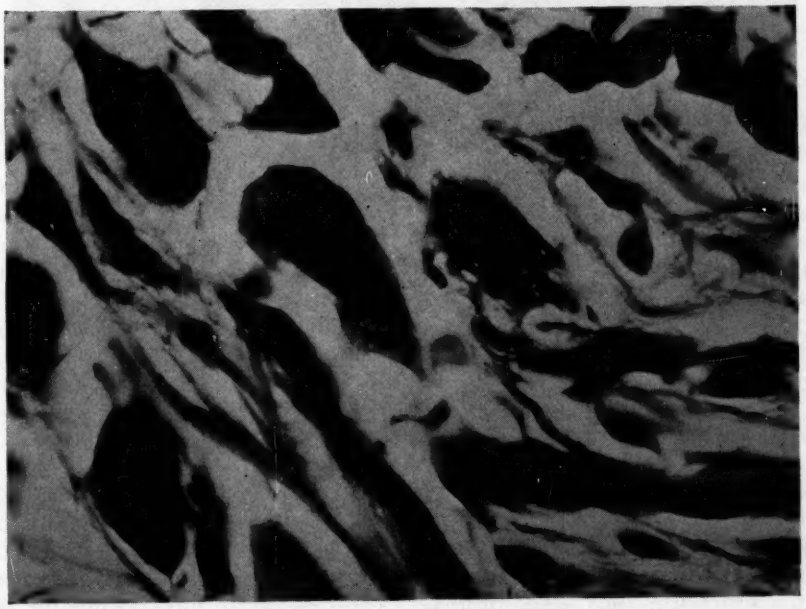


Fig. 2.—The granularity and the pleomorphic character of the cells is well depicted here. No cross striations are in evidence (hematoxylin and eosin, ×950).

high magnifications many of these spindle cells were seen to be large and eosinophilic with straplike masses of reddish-pink granular cytoplasm (Fig. 2). The nuclei of these cells were centrally located, round to oval in shape, moderately hyperchromatic and somewhat vesicular. Search of many fields failed to show the presence of longitudinal or of cross striations within the cells.

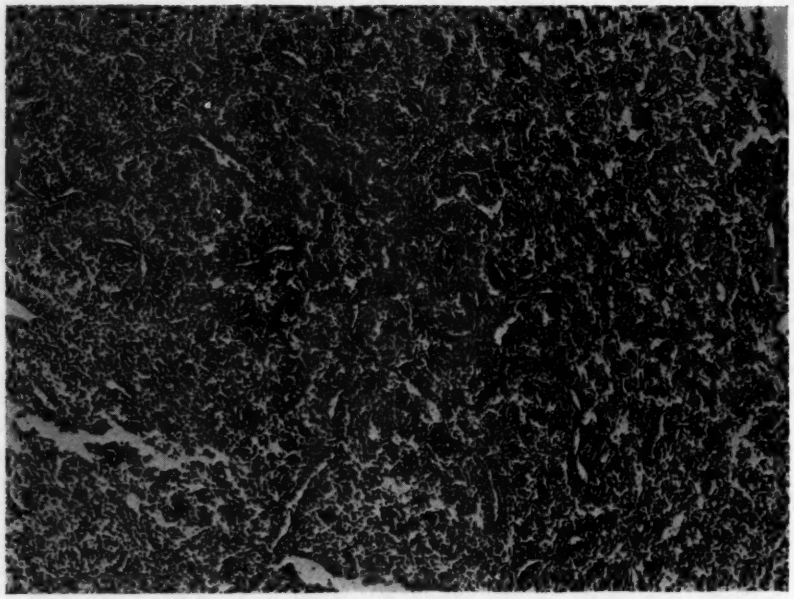


Fig. 3.—Low-power aspect of tumor after second recurrence. The tumor cells are disposed about innumerable spaces (hematoxylin and eosin, ×50).

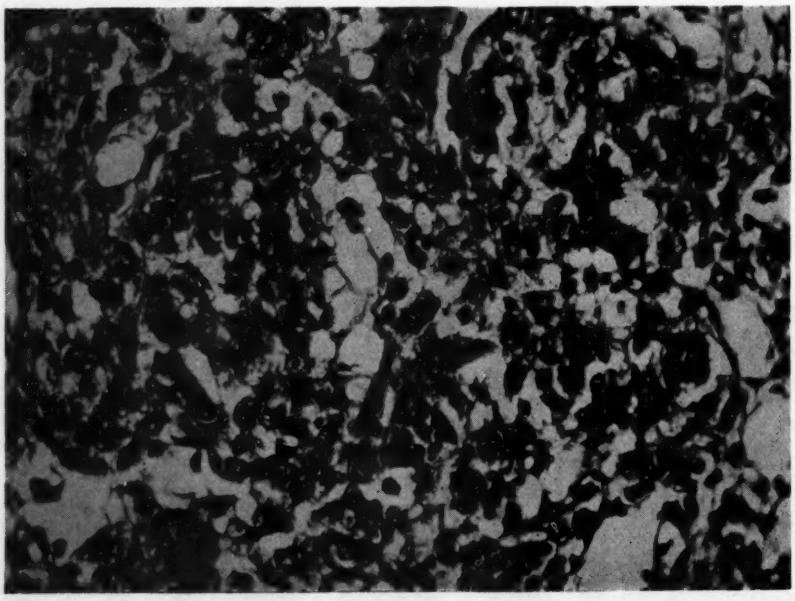


Fig. 4.—The constituent cells here are small and round to spindle in shape; they exhibit large dark-staining nuclei and prominent nucleoli. They appear to form the walls of the blood vessel-like spaces (hematoxylin and eosin, ×320).

Intermingled with these elements were small spindle cells with much reduced cytoplasmic content but with relatively large nuclear volume (Fig. 1). The nuclei of these cells were hyperchromatic and mitotic spindles were fairly easy to find. Cytoplasm was not particularly eosinophilic and on casual inspection the tumor might seem to be composed of two distinct cellular elements. However, fair numbers of transitional forms were observed so that cytologic connections could be traced from the smallest spindle cell to the largest granular units. That the granular cells were at the mature end of the scale was evidenced by their failure to exhibit mitotic activity.

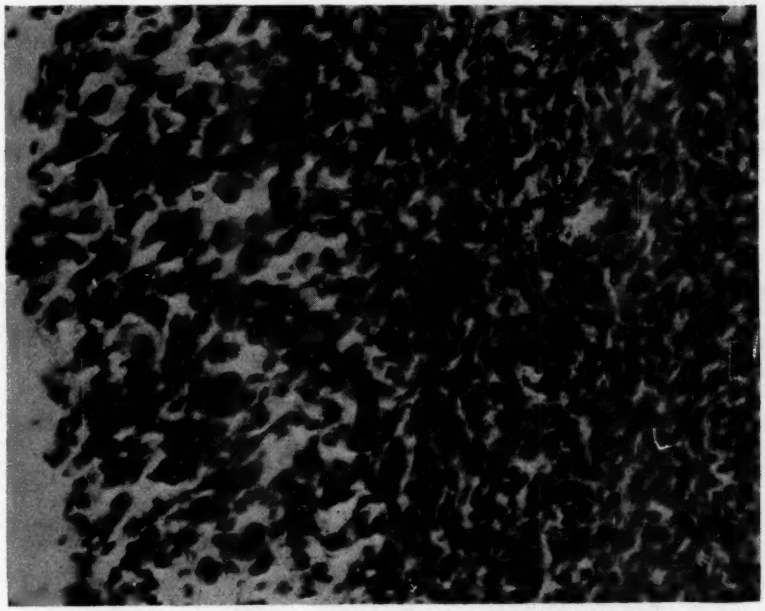


Fig. 5.—Transitions between endothelium-like elements and pleomorphic myoblasts are apparent (hematoxylin and eosin, ×250).

The final recurrence provided the most interesting picture. The bulk of the tumor was composed of small spindle cells as described, but they were disposed around innumerable small blood vessel-like spaces (Fig. 3). The lining of these spaces was, in fact, an investment of tumor cells. In other words, the neoplasm now displayed the features of a malignant angioma or angioendothelioma (Fig. 4). Such was the diagnosis at this time, and it was not until re-examination of fixed sections that the granular cell component became obvious. Transitions between the endothelium-like cells and the granular myoblasts could again be traced (Fig. 5). The tumor was seen to invade lymphatic spaces including perineural lymphatics, and one of the structures labelled "inguinal node" was so overrun by metastatic invasions that it was no longer recognizable as a node microscopically.

Comment

Four questions need clarification regarding the condition under discussion: 1. Is myoblastoma an entity? 2. Is it a true neoplasm and, if so, is it benign or malignant? 3. What is its origin? 4. What are the nature and etiology of the changes so frequently observed in squamous epithelium when it is encroached upon by an underlying myoblastoma? Around these four questions controversy has raged.

Regarding the first question we may say that although distinguishing clinical characteristics do not exist, with the exception perhaps of the peculiar tendency toward involvement of the tongue and gums, the histopathologic features of myoblastoma are fairly distinctive. The diagnosis depends upon the pathologic examination which should demonstrate the presence of large granular eosinophilic cells, resembling muscle cells but lacking cross striations. Many consider these features sufficient to call the condition an "entity." However, as Willis[19] has forcefully pointed out, deductions based on histologic resemblances do not prove identity. He felt that, since the "muscular nature is unproved," the term "myoblastoma" should be discarded to avoid perpetuating "several dubious and erroneous concepts."

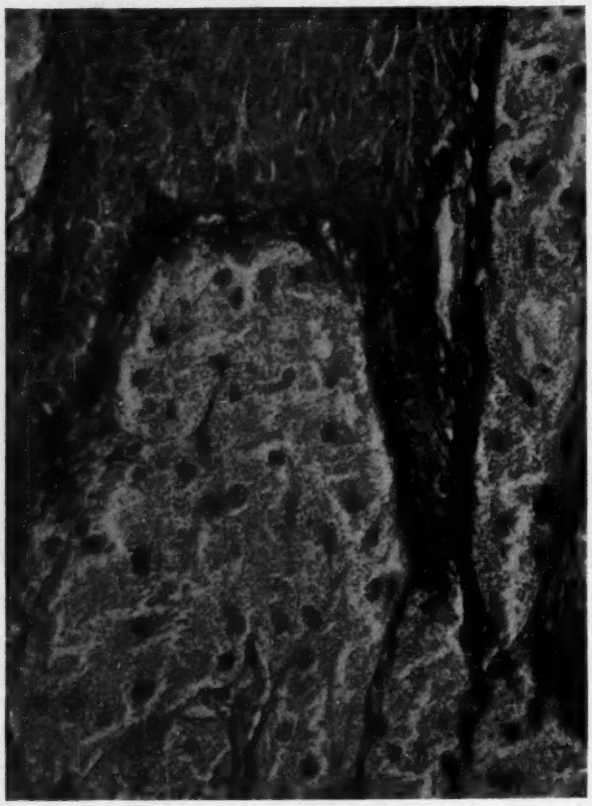


Fig. 6.—Myoblastoma vulvae, uniform cell type, previously reported by Murphy, Dockerty, and Broders. Granularity is a pronounced feature of the cytoplasm. The overlying epithelium is normal (hematoxylin and eosin, ×365).

With reference to its neoplastic nature, opinion again is divided. When, as in the case of lingual myoblastomas, the lesion is seen to lie in juxtaposition to striated muscle, degenerative changes are oftentimes present in the latter and transitions between these degenerating elements and myoblastoma cells have been traced to the satisfaction of many.[1, 2, 13] It was Abrikossoff's[2] opinion that these changes signified neoplasia of regenerating muscle (Fig. 6). Others feel that these alterations are truly degenerative and that the so-called uniform cell type of myoblastoma is not a neoplasm.[5] Mitosis is usually lacking; growth is extremely slow. Yet Khanolkar,[7] to cite one observer, reported metastasis from a seemingly innocent-appearing lesion of this type. The "pleomorphic variant" (if we are allowed to use the term) is often manifestly neoplastic and exhibits recurrence and metastasis.

Still others express the view that the uniform cell type of myoblastoma is a protein storage disease akin to xanthomatosis,[10] whereas the pleomorphic type is in reality an atypical rhabdomyosarcoma. It is our impression, however, from reading the literature, that the tumors designated as "malignant myoblastomas" carry a much better prognosis than that associated with rhabdomyosarcoma. This fact alone would seem to justify what many call an "artificial separation" of the two.

As regards histogenesis, an origin from pre-existing voluntary muscle would seem logical for the large group of lingual myoblastomas. Striated muscle, however, is not indigenous to the skin, and perhaps 30 per cent of the tumors occur in this location. In some of these cases, a derivation from embryonic misplaced myoblasts has been postulated but never demonstrated.[9] Origin from histiocytes engaged in protein storage has been suggested as an alternative hypothesis.[10] Fust and Custer,[4] in a recent study of some 52 cases from the Army Medical Museum, concluded that the growths were neurogenic and related to neurofibromas. All of their tumors were of the uniform cell type, the authors maintaining that pleomorphic examples of the condition were rhabdomyosarcomas. Montgomery[12] was unable to confirm their findings in regard to neurogenesis.

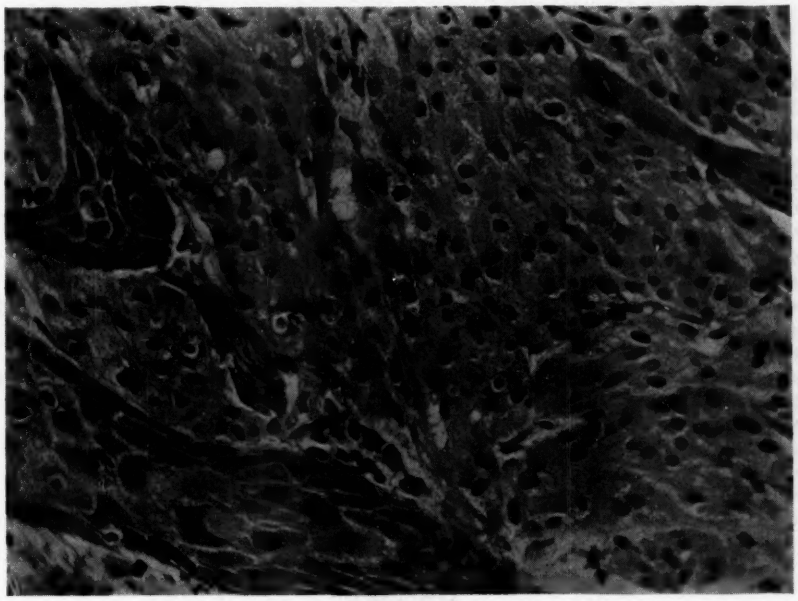


Fig. 7.—Uniform type of myoblastoma vulvae. The appearance of the myoblastoma cells is similar to that depicted in Fig. 6, but the overlying epithelium is hyperplastic (hematoxylin and eosin, ×200). (Dr. James Y. Clarke of Sioux Falls, S. D., kindly consented to let us use this illustration.)

In a previous communication[13] the view was supported[11] that myoblastomas, particularly the pleomorphic variant, might arise from pluripotent cells. Both Montgomery[12] and Wasserman[18] have observed apparent transitions from benign endothelial cells to the uniform type of myoblastoma which occurs along the growing margins of cutaneous growths. Our own case furnishes corroborative evidence in the production of the tumor which exhibited features of malignant pleomorphic myoblastoma and angioendothelioma.

Finally, one of the most baffling mysteries connected with this tumor consists of a remarkable atypical proliferation of squamous epithelium over many of the superficially placed tumors. Such proliferation is noted almost routinely

with lingual myoblastomas, but it also is fairly common in subcutaneous growths, including two of the vulvar tumors reported in the literature (Fig. 7). In most tumors of this type, atypical proliferation of the squamous epithelium has been regarded as representing benign pseudo-epitheliomatous hyperplasia; in others it has been interpreted as being frank epidermoid carcinoma. However, none of these "accessory" growths has ever metastasized. Neurofibromas and other types of subcutaneous new growths induce atrophic changes in the overlying squamous epithelium, myoblastoma being unique in its induction of hyperplasia. Allen's[3] suggestion that myoblastomas elaborated some material which simulated epithelial cells should be worthy of investigation.

Summary

An unusual malignant vulvar tumor has been described which we feel is a pleomorphic myoblastoma. In its recurrence and metastasis the neoplasm exhibited transitions to an angioblastic type of growth. Such metaplasia can be satisfactorily explained on a theory of origin from an ancestry of pluripotent mesenchymal cells. Five other vulvar myoblastomas which came to our attention were all of the uniform cell type and all proved to be benign.

References

1. Abrikossoff, A.: Virchows Arch. f. path. Anat. 260: 215, 1926.
2. Abrikossoff, A. I.: Virchows Arch. f. path. Anat. 280: 723, 1931.
3. Allen, A. C.: Arch. Dermat. & Syph. 57: 19, 1948.
4. Fust, J. A., and Custer, R. P.: Am. J. Clin. Path. 19: 522, 1949.
5. Gander, Georges: Bull. Assoc. franç. p. l'étude du cancer 24: 56, 1935.
6. Kern, A. B., Kaufman, J. J., and Combes, F. C.: Arch. Dermat. & Syph. 62: 109, 1950.
7. Khanolkar, V. R.: Am. J. Path. 23: 721, 1947.
8. Klemperer, Paul: Am. J. Cancer 20: 324, 1934.
9. Klinge, F.: Verhandl. d. deutsch. path. Gesellsch. 23: 376, 1928.
10. Leroux, R., and Delarue, J.: Bull. Assoc. franç. p. l'étude du cancer 28: 427, 1939.
11. Meyer, Robert: Virchows Arch. f. path. Anat. 287: 55, 1932.
12. Montgomery, H.: Personal communication to the authors.
13. Murphy, G. H., Dockerty, M. B., and Broders, A. C.: Am. J. Path. 25: 1157, 1949.
14. von Szathmary, Z.: Magyar orvosi arch. 38: 260, 1937.
15. von Szathmary, Z.: Zentralbl. f. d. ges. Gynäk. u. Geburtsh. 114: 371, 1937.
16. Tamis, A. B., and Kowles, J. J.: AM. J. OBST. & GYNEC. 42: 543, 1941.
17. Tonelli, Luigi: Arch. "de Vecchi" per anat. pat. e med. clin. 5: 1, 1943.
18. Wasserman, R. B.: Personal communication to the authors.
19. Willis, R. A.: Myoblastoma. In: Rupert, A.: Pathology of Tumours, London, 1948, Butterworth & Co. Ltd., pp. 743-747.

Discussion

DR. EUGENE H. COUNTISS, New Orleans, La.—Drs. Sadler and Dockerty are to be commended for their exhaustive clinical and pathological study of an individual case of myoblastoma, thus adding to a better understanding of a rare and confusing type of tumor. The case report stresses the importance of adequate excision of vulvar tumors, followed by careful pathologic study. We often fail to realize the seriousness of small and innocent-looking lesions. I have had the opportunity of studying sections of only four myoblastomas, originating respectively in a toe, abdomen, neck, and vulva. The histological appearance of some of these sections shows a striking resemblance to tumors of endothelial origin. Particularly following secondary infection, an area may be practically indistinguishable from sarcoma. The age of a tumor, as well as the outstanding pathology, may alter the diagnosis. Thus in the first recurrence and microscopic study, where cystic changes were prominent, a diagnosis of infected epidermoid cyst was originally made. In the light of ensuing events,

restudy leads to the true nature, or myoblastoma. A more frequent example of the effect of duration of malignancy is in adenocarcinoma of the fundus uteri, where extensive cell infiltration of the stroma may simulate sarcoma.

There can be no argument as to the possibility of origin of myoblastomas from pluripotential mesenchymal cells. In malignant myoblastoma vulvae, the following facts seem pertinent:

1. The homologue of cremasteric muscle may be found in the labia.
2. Misplaced congenital remnants are more prone to neoplastic changes, wherever their location.
3. The nature of myoblasts gives them the potentiality of malignant transformation.

Original Communications

THE MORPHOLOGIC BASIS OF OVARIAN FUNCTION

I. The Development of Methods for Quantitative Measurement of Specific Ovarian Tissues*†

HOWARD C. TAYLOR, JR., M.D., PATRICIA MCAULEY, B.A., AND EARL T. ENGLE, PH.D., NEW YORK, N. Y.

(From the Obstetrical and Gynecological Department of the College of Physicians and Surgeons, and from the Sloane Hospital for Women, The Columbia-Presbyterian Medical Center)

THE morphologic characteristics of the endometrium have been related to functional disorders of fertility and menstruation with some success. Such entities as cystic hyperplasia, irregular shedding, and various degrees of atrophy or of incomplete progestational preparation are quite well established and have a practical clinical importance.

By contrast, the morphologic basis of ovarian dysfunction, is, with the exception of the extreme degrees of atrophy, not understood and scarcely explored. The reasons for the difference in the development of the knowledge of these two organs are two: First, in the simple functional disorders, the ovary is usually inaccessible to biopsy. Second, the ovary is rather unique among the tissues of the body in that, on account of the variable development of the functioning tissue in different parts of its substance, no single section of the ovary can be accepted as representative of the whole. The first difficulty can be overcome only by patient waiting for representative cases in which sudden death or justifiable surgery makes material available. The second problem must, in our opinion, be met by the development of a method by which the different functioning or function-capable tissues of the ovary may be completely measured.

This presentation is then a preliminary report on our attempts to develop a practical method for the quantitative morphologic evaluation of ovarian function.

Certain previous attempts have been made in this direction. The earliest workers, such as Henle and Sappy in 1873 and Meier in 1906, studied ovaries from various age groups but were interested only in the number and relative size of the follicles. In 1921, however, Dr. Paul Höggstrom, using a method similar to the first of the methods we are to report, completely examined the two ovaries of a 22-year-old woman who had died under anesthesia.

*Presented at the Conference on Testis and Ovary, Eggs and Sperm, for the Committee on Human Reproduction of the National Research Council, held on May 23, 1950, at the Hotel Commodore, New York City.

†Aided by grants from the John and Mary R. Markle Foundation and by a grant recommended by the Committee on Growth of the National Research Council to the American Cancer Society.

In Höggstrom's study, the ovaries were embedded in celloidin, sectioned at 36 μ and every tenth section was retained for study. Each section was heavily stained with hematoxylin and eosin and the projected image traced. Using a polar planimeter, the general areas of tunica albuginea, zones of primordial and Graafian follicles, and the vascular zone were measured from the tracings. Dr. Höggstrom counted and classified the Graafian and primordial follicles into 27 groups according to the size of the diameters, as for example those less than 50 μ, those from 50 to 100 μ, and so forth. For the smaller Graafian and the primordial follicles, he used a microscope equipped with an ocular micrometer to determine diameters. In this manner, the atretic follicles, corpora lutea and corpora albicantia were also counted and classified. From Dr. Höggstrom's work it appeared possible, by measuring areas of a series of sections throughout an ovary, to determine the volumes and thence the percentages of the ovarian components.

Mathematical Principles

In the present study, two methods were employed, each depending on the same basic mathematical principles. These require a brief statement.

All ovaries are serially cut at 10 μ and sections retained for measurement at regular intervals. The total area of the ovary and the areas of all components, such as Graafian and atretic follicles, theca, granulosa, corpora lutea and ablicantia, are measured on each section. The resulting figures from all sections are substituted in Simpon's Rule for determining the volume of an irregular object, or in a variation of this rule (Table I).

Simpson's Rule: (for even number of sections or readings)

$$A \text{ or } V = \frac{1}{3} h \left[(y_0 + y_n) + 4 (y_1 + y_3 - \cdots + y_{n-2}) + 2 (y_2 + y_4 + \cdots + y_{n-1}) \right]$$

A equals area
V equals volume
h equals distance between sections or readings
y equals area or linear measurement

Variation (Durand's Rule): (for odd number of sections or readings)

$$A \text{ or } V = h \left[0.4 (y_0 + y_n) + 1.1 (y_1 + y_{n-1}) + y_2 + y_3 + \cdots + y_{-n2} \right]$$

If "h" is small enough, the slope of the curve of the ovarian surface can be considered a straight line, and the dimensions in the center of this small area can be taken as the average for the area. In effect, the surface of ovary is reduced to a series of rectangles of known dimensions.

Procedure A. Planimeter Method

The first method used in this study was rather similar to that employed by Dr. Höggstrom, although we were not familiar with his work when we began our own study. The ovaries were fixed in Bouin's solution and then embedded in paraffin. The entire ovary was cut at 10 μ and every twentieth section was retained for measurements. Each section was deeply stained with hematoxylin and eosin in order to make it possible to differentiate tissue components macroscopically.

To measure those components large enough to observe without a microscope, sections were first placed in a photographic enlarger and magnified about seven times, and the projected image was carefully traced (Fig. 1). Plans similar to the one shown here (Fig. 2) were obtained for every retained section. The areas of all functioning portions of each tracing were determined by employment of a compensating polar planimeter. This is an instrument (Fig. 3) used for measuring small areas directly in units which must be converted to square centimeters. It consists of two arms, one of which is provided with a stylus for tracing the perimeter of the figure being measured; the other has a pinpoint for anchoring the instrument at some point outside the figure. The arm with the stylus carries a graduated wheel with a vernier calibrated so that the area can be read directly. The area of the figure is known to be equal to the length of the arm multiplied by the radius of the wheel and by the angle through which the wheel rotates, otherwise expressed by the formula $A = lr\phi$, where ϕ is the angle through which the wheel rotates. By the use of a calibrated arm which traces a known area, the constant for any setting of the arm and tracing bar can be found. The planimeter was used in this manner to measure the total area of the ovary and areas of all follicles, theca, corpora lutea, and corpora albicantia in the sections traced.

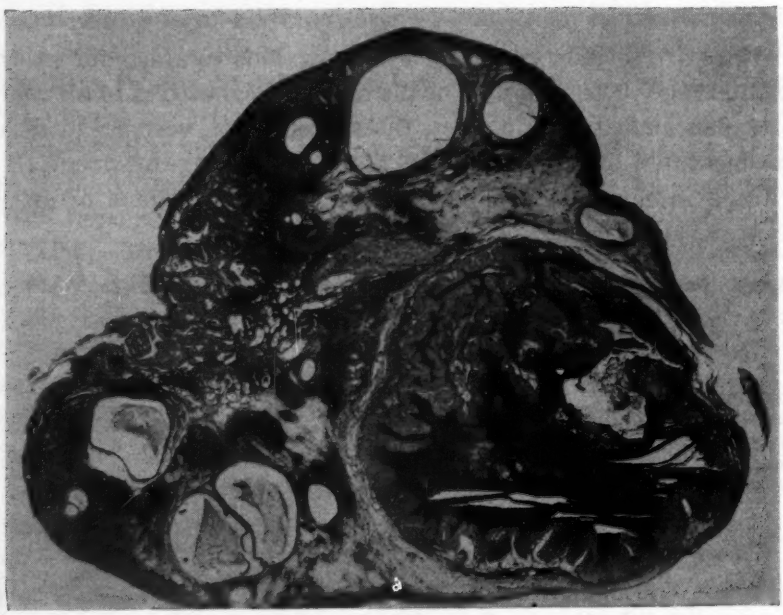


Fig. 1.—Projected image of normal ovary for tracing.

All components not easily visible under the enlarger, such as primordial follicles and granulosa, were measured by the use of a microscope equipped with an ocular micrometer. Linear measurements of the object were obtained with the micrometer at regular intervals and were substituted in Simpon's Rule, which was in this instance first used to obtain the areas of components in each section. The areas for each section were then totaled and the totals also substituted in the equation to determine total volumes.

This method of study has proved accurate, but laborious almost to the point of impracticality. Five months were required to complete the study of a single ovary of a young woman.

Procedure B. Calibrated Graph Method

During the last year, efforts have been made toward the simplification and improvement of the method. A calibrated graph has been substituted as the basic method of measurement and a projecting microscope is now used instead of the ocular micrometer for the initial measurements.

In practice, to obtain the total area, the slide is placed in the photographic enlarger and the image, magnified ten times, is projected on a calibrated graph from which linear measurements can be read directly in millimeters. For the finer components, a projecting microscope is used with another calibrated graph, the latter mounted on a sliding board whose distance can be varied when different objectives of the microscope are employed (Fig. 4). Linear measurements are again obtained from the projected image in millimeters and substituted in the same formula to obtain areas as employed in the first method. The areas for both the total ovary and for its components are then used in the calculations to determine volumes.

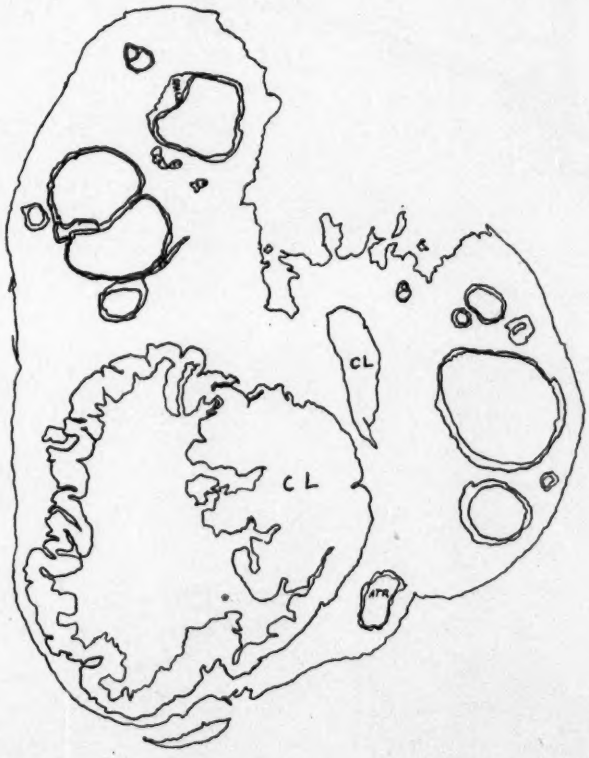


Fig. 2.—Traced pattern of normal ovary for measuring.

To check the validity of this method, a circle of paper having a known radius of 1 cm. was cut into odd-shaped pieces similar to the ovarian sections and mounted on slides (Fig. 5). The new method, when employed to reconstruct the original area, showed an error of 1.2 per cent; the old, of 3.53 per cent. Both errors in measurement are probably smaller than variations due to circulatory states of the ovary and to methods of preparation.

Reduction in Number of Sections.—A reduction in the total number of sections which must be studied has also proved to be justifiable. It has been

found that, if the interval between the sections is increased from 20 sections to 50, a variation of less than 1 per cent is obtained. The justification of reducing the number of sections is illustrated in Table I, in which the total volume of an ovary of a 57-year-old woman has been calculated first by 39 slides at 20 sections

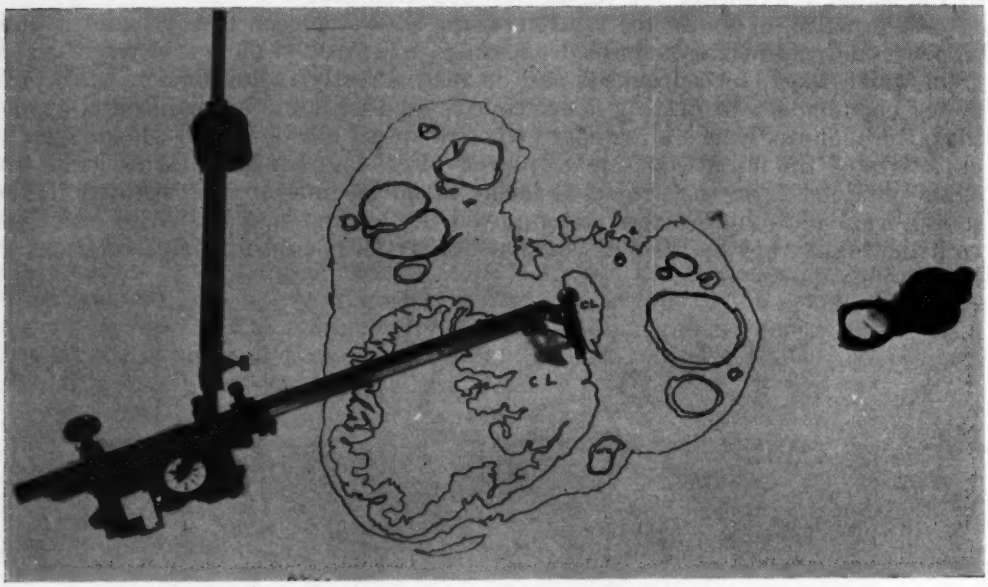


Fig. 3.—Measurement of specific ovarian tissue by means of the planimeter.

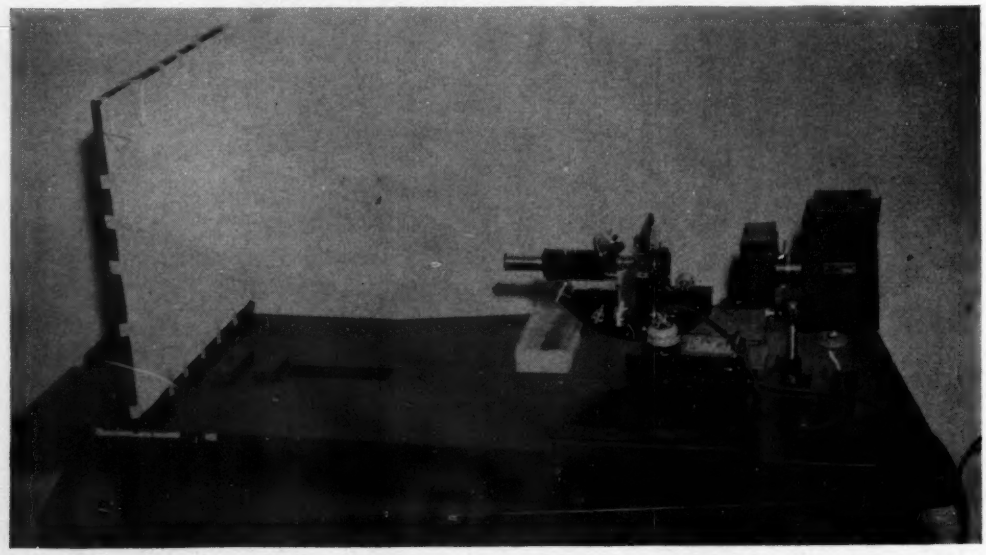


Fig. 4.—Apparatus for measuring specific ovarian tissues by means of the calibrated graph.

apart (or 200 μ) and then by two series, A and B, of the same 39 slides. In Series A, the area of every fourth slide starting with the first is used to calculate the total volume. This yielded a total of ten slides and an interval of 80 sections (or 800 μ). The deviation from the original calculation with 39 slides was 0.67

per cent. With the second series (Series B) the area of very fourth slide, starting with the second slide in the original series, was used for calculating the total volume. The deviation was only 0.29 per cent.

TABLE I. JUSTIFICATION OF REDUCING NUMBER OF SECTIONS. TOTAL VOLUME OF OVARY OF A 57-YEAR-OLD WOMAN

NUMBER OF SLIDES DISTANCE APART	TOTAL VOLUME C.C.	PERCENTAGE DEVIATION BETWEEN ORIGINAL METHOD AND SERIES A OR B
Original Method.— 39 Slides Every 20th Section Measured	0.574	
Series A.— 10 Slides Every 4th Slide beginning with the 1st (Every 80th measured)	0.578	+0.67
Series B.— 10 Slides Every 4th Slide beginning with the 2nd (Every 80th measured)	0.576	+0.29

Fixation and Embedding.—The ovaries were still fixed in Bouin's medium, but a double embedding technique with paraffin and celloidin is now used to minimize shrinkage. Due to the large size of some specimens and the tough outer capsule, proper infiltration of the ovaries with the embedding medium has proved a major problem. This difficulty has been almost entirely overcome by the use of a vacuum chamber for infiltration with celloidin for varying time periods, depending upon the size of the ovary. The sections are all cut on a rotary microtome at 10 μ.

MEASUREMENTS OF A KNOWN AREA BY METHODS A AND B

	AREA (cm^2)	% DEVIATION
True Area	3.1416	
Method A	3.0345	- 3.53%
Method B	3.1801	+ 1.21%

Fig. 5.—Test of accuracy of methods, by measurement of known area by planimeter (Method A) and by calibrated graph (Method B).

Comparison of Methods.—This new method, requiring about a quarter of the former time to complete the study of an ovary, is found to give results checking very closely with those of the previous method (Table II). The volume of a

TABLE II. TOTAL VOLUME OF ONE OVARY MEASURED BY BOTH METHODS (10 SECTIONS)

METHOD A AREAS OBTAINED FROM TRACINGS BY USE OF PLANIMETER	METHOD B AREAS DERIVED MATHEMATICALLY FROM PARALLEL LINEAR MEASUREMENTS	PERCENTAGE DEVIATION
0.578 c.c.	0.579 c.c.	0.17

single ovary of one patient was found to be 0.578 c.c. by the old method, and 0.579 c.c. by the new method. Efforts must doubtless be made still further to reduce the time required if this procedure is to attain real practical value.

TABLE III. OVARIES OF A 27-YEAR-OLD WOMAN WITH CARCINOMA OF THE CERVIX

		TOTAL VOLUME	VOLUME OF FOLLICLES	VOLUME OF THECA	VOLUME OF FOLLICULAR CAVITY	CORPUS	GRANULOSA
Ovary No. 1 with corpus luteum	c.c.	9.897	1.027	0.187	0.840	1.654	0.006
	per cent	100.00	10.38	1.9	8.5	16.9	0.06
Ovary No. 2	c.c.	5.491	0.615	0.148	0.467	0.603	0.018
	per cent	100.00	11.2	2.7	8.6	10.9	0.32
Totals	c.c.	15.388	1.642	0.335	1.307	2.258	0.024
	per cent	100.00	10.66	2.18	8.49	14.67	0.15

Preliminary Results

The work up to this time has been devoted largely to the development of a method. A few perhaps interesting, but not yet significant, data have come to light during this process.

a. The Ovaries in a Patient With Carcinoma of the Cervix.—

The first pair of ovaries measured were those of a 27-year-old woman subjected to radical hysterectomy for cancer of the cervix (Table III). These ovaries were measured by the first method and serve to show general relationships which are perhaps the average for normal women in the middle of their reproductive period of life.

In one ovary there was a large, recent corpus luteum which, of course, very much affected the proportions between the total functioning tissues in that ovary. The final line of this table shows that the corpus luteum tissue occupied nearly 15 per cent of the total tissue of the two ovaries and the follicles about 10 per cent. The greatest part of the follicular volume is, of course, made up of follicular cavity, while only very small percentages of the entire ovary are represented by the functioning theca and granulosa cells.

b. Ovaries in the Menopause (Table IV).—

To afford an extreme contrast, the ovaries of a woman of 57, operated upon for fibroids some years after the menopause, were examined. Here no functioning tissue was present, but the total bulk of corpus albicans, 23.5 per cent, formed a proportion to the whole interestingly similar to that of the actively functioning tissue in the younger woman. This study was also made by the first or planimeter method.

TABLE IV. OVARIES OF A 57-YEAR-OLD WOMAN WITH FIBROMYOMA UTERI

		TOTAL VOLUME	CORPUS ALBICANS
Ovary No. 1	c.c.	0.574	0.148
	per cent	100.00	25.75
Ovary No. 2	c.c.	0.780	0.170
	per cent	100.00	21.73
Totals	c.c.	1.355	0.318
	per cent	100.00	23.44

c. Ovary of a Menstruating Woman of 57 (Table V).—

As evidence of the differences which may obviously exist between the ovaries of women of the same age, the measurements of a single ovary obtained from another woman still menstruating at the age of 57 are presented. These measurements were obtained by our second method, that is to say, with the use of the calibrated graph. They show that, whereas remnants of functioning tissue, the corpus albicans, are the predominant elements in the specific ovarian tissues, nevertheless follicles are still present with luteal, thecal, and granulosal cells.

TABLE V. ONE OVARY OF A 57-YEAR-OLD WOMAN WITH CONTINUING MENSTRUATION

		TOTAL VOLUME	VOLUME OF CORPUS ALBICANS	VOLUME OF CORPUS LUTEUM	VOLUME OF FOLLICLES	VOLUME OF FOLLICULAR CAVITY	VOLUME OF THECA	VOLUME OF GRANULOSA
Right ovary	c.c.	3.405	0.378	0.190	0.033	0.015	0.012	0.035
	per cent	100.00	11.09	5.57	0.96	0.44	0.35	0.001

d. Contrast of Ovaries From Two Women of 57 (Table VI).—

The next table brings into sharper contrast the morphologic evidence of past and present ovarian function in two women of 57, the one after the menopause, the other still menstruating.

TABLE VI. CONTRAST IN OVARIES OF TWO WOMEN OF 57 WITH RELATION TO MENSTRUATION

		TOTAL VOLUME	VOLUME OF CORPUS ALBICANS	VOLUME OF CORPUS LUTEUM	VOLUME OF FOLLICLES	VOLUME OF FOLLICULAR CAVITY	VOLUME OF THECA	VOLUME OF GRANULOSA
Case in menopause	c.c.	0.574	0.148	0	0	0	0	0
	per cent	100.00	25.75					
Case still menstruating	c.c.	3.405	0.378	0.190	0.033	0.015	0.012	0.001
	per cent	100.00	11.09	5.57	0.96	0.44	0.35	0.035

e. Contrast in Ovaries of Two Menstruating Women at Opposite Age Periods of Ovarian Life.—

The probable range of morphologically determinable differences in ovarian function of women with clinically normal menstrual periods is demonstrated in the next table (Table VII). Here are shown the results of the quantitative determination of the functioning constituents of two women, both menstruating normally, one at the age of 27, one at the age of 57.

TABLE VII. CONTRAST IN OVARIES OF MENSTRUATING WOMEN AT AGES OF 27 AND 57 YEARS

		TOTAL VOLUME	VOLUME OF CORPUS ALBICANS	VOLUME OF CORPUS LUTEUM	VOLUME OF FOLLICLES	VOLUME OF FOLLICULAR CAVITY	VOLUME OF THECA	VOLUME OF GRANULOSA
Aged 27	c.c.	5.491		0.603	0.615	0.467	0.148	0.018
Ovary No. 2	per cent	100.00		10.9	11.2	8.6	2.7	0.32
Aged 57	c.c.	3.405	0.378	0.190	0.033	0.015	0.012	0.001
Right ovary	per cent	100.00	11.09	5.57	0.96	0.44	0.35	0.035

The figures show that, in spite of identical clinical manifestations of ovarian function, there are great differences in morphology and presumably in capacities for function. The younger ovary is nearly twice as large and, furthermore, the percentage of the ovary occupied by functioning tissue is much greater. This is evident in all constituents, luteal, thecal, and granulosal. Furthermore, the follicular space in the younger ovary is very much larger.

The data in these two ovaries are what might be expected, but they serve as an example of degrees of difference in function, as measured by morphology, which may underlie a clinically identical menstrual status.

Summary and Conclusions

This report is concerned with steps in the development of a method for evaluating ovarian function on the basis of complete quantitative studies of the different specific ovarian tissues. Such a method seems essential in view of the imperfection of present indirect methods of studying ovarian function which depend on endometrial histology or the assay of urinary steroids.

The method needs further simplification, perhaps by the demonstration that still fewer sections need be examined. It likewise requires a combination with histological staining techniques which will define more accurately the function or potential functions of the specific tissues that are being quantitatively evaluated.

When perfected, the method seems to have a rather wide application in the classification of the perhaps rather large group of functional disorders of the ovary. These include at least the so-called cystic "transformations" or "degenerations" of the ovary of which there are probably several sorts. The method should also be of use in settling the still-disputed question of whether the ovaries associated with fibromyomas or other uterine tumors are in any way abnormal.

References

Häggström, Paul: Zahlenmässige Analyse der Ovarien eines 22—jährigen gesunden Weibes, Upsala Läkareförenings Förhandlengar n. f. 26, Häft 5-6, Festskrift för Professor J. Aug. Hammor, no. XV, 52 pp., 1921.

Henle, Friedrich Gustav Jacob: Handbuch der systematischen Anatomie des Menschen, 2. Bd., 2. Auflage, 1873, Braunschweig.

Meyer, Robert: Arch. f. Gynäk. 100: 1, 1913.

Meyer, Robert, and Ruge, Carl, II.: Zentralbl. f. Gynäk. 37: 50, 1913.

Sappey, Marie-Philibert—Constant: Traité d'anatomie descriptive, ed. 2, Paris, 1874, vol. 4, chap. 4, section 4, p. 683.

MICROSCOPIC OBSERVATIONS OF THE DEVELOPMENT OF THE HUMAN PLACENTA

B. S. KLINE, M.D., CLEVELAND, OHIO

(From the Department of Laboratories, Mt. Sinai Hospital)

PRESENT-DAY standard textbooks of embryology and obstetrics (e.g., Patten, Novak) present the development of the human placenta as a growth of villi and trunks, regional to one another but independent of each other, much like a growth of trees in a thicket and with all the structures in most of the organ normally intact until the end of pregnancy. Stieve,[10, 11] however, by microscopic study and enlarged reconstructions of the human placenta, found the villi and trunks adherent to one another in the second half of pregnancy and the organ spongelike in construction.

According to Stieve, villus trunks grow from the chorion plate in the first two months of pregnancy and unite with the basal plate or other fastening trunks. Later, branches bud off in all directions from the villus trunks and in the second half of pregnancy, especially, these draw toward other placental structures and unite with them. At the site of attachment of villus or trunk to villus or trunk, the syncytium disappears first, the stroma of one structure impinges on that of the other and the blood vessels of the two uniting parts join by anastomosis so that the fetal blood flows from one villus branch into the other. Later the sites of anastomosis are unrecognizable and the placenta has the appearance of a sponge. The process goes on to the end of pregnancy. Stieve noted fibrin masses interposed between individual villi and believed such clumps hindered the union of the fetal structures.

In a study previously reported,[5] microscopic observation of 117 human placentas of cases of normal pregnancy of four months or less showed villi and trunks completely independent of one another, and almost without exception, wholly intact.

Material

In 213 placentas in the second half of normal pregnancy, however, breaks in the surface of numerous villi and trunks are observable, covered by fetal blood or recent or old blood clots which extend a variable distance and in all directions from their source. These clots bind villus or trunk to one or more villi or trunks. The recent clots appear to be molded, in great part, into shapes resembling portions of villi and trunks. In many places the cellular elements of the clots are no longer present and cylinders of fibrin only remain. In places these are covered by syncytium extending from intact portions of regional villi or trunks. In other places, connective tissue from regional villi or trunks is observable extending into the fibrin cores and, in some portions, completely organized structures almost or entirely indistinguishable from similar residual villi and trunks are present. These findings indicate the

capacity of fetal tissues to organize blood clots as well as adult tissues do. They also support the contention of Stieve[10] that many of the villi and trunks are firmly bound to each other in the second half of pregnancy and that, at this time, the organ resembles a sponge and not a thicket of miniature trees.

Much has been written in the past fifty years about the abundant fibrin found in the placenta in the second half of pregnancy. Excellent reviews of the observations and opinions of numerous investigators were reported by Kalima[4] (1912), Grosser[3] (1925), Sidall and Hartman[9] (1926), and Wislocki and Bennet[12] (1943). It has been generally accepted that the fibrin masses in intervillous spaces and those adherent to fetal structures are entirely maternal in origin.

Evidence that the fibrin masses are of fetal origin is presented in two previous reports.[5, 6] Especially convincing are the microscopic findings in 2 of 13 placentas of fatal cases of erythroblastosis fetalis. In one of these 2 cases, the baby, of 8½ months' pregnancy, lived 33 minutes and the other, of 7½ months pregnancy, lived 25 minutes. Numerous sections of the placentas show clearly many breaks in the surface of villi and trunks. Covering them, in places, there is fetal blood with many intact nucleated red blood cells, in places, very recent and recent blood clots with intact and/or degenerating nucleated fetal red blood cells, apparently the remains of fetal hemorrhages that occurred at, or shortly before, expulsion. These two placentas, furthermore, in many places, show binding of villus or trunk to villus or trunk by fetal blood clots, many of which exhibit transitional changes to hemoglobin-stained fibrin masses, and unstained fibrin masses. Many fibrin masses are observable covered in part or wholly by syncytium, extending from intact regional residual syncytium. Many show further organization by connective tissue extending from intact residual stroma of regional villus or trunk with resultant new structural units almost or completely indistinguishable from residual villi and trunks or portions thereof.

On careful microscopic examination, fetal hemorrhages similar to those observed in the two cases of erythroblastosis fetalis were found in the placenta of each of the 13 additional cases of this disorder. In these, however, 11 of the babies were stillborn and macerated. Nucleated red blood cells were no longer detectable in the fetal hemorrhages (owing to autolytic changes). Fetal hemorrhages from villi and trunks were likewise found on microscopic examination of the placenta of each of two infants with mild cases of erythroblastosis fetalis who recovered and in each of 213 cases in the second half of normal pregnancy. Figs. 5, 6, and 7 show clearly formation of new placental tissue by organization of the fibrin of fetal blood clots.

Microscopic study of the placentas in the 15 cases of erythroblastosis fetalis and in the 213 cases in the second half of normal pregnancy indicates that the changes described above result from damage to peripheral blood vessels of villi and trunks and to the regional trophoblast. The sequence suggested by the study is: (a) damage to the small peripheral blood vessels, and to the regional trophoblast (by excretory products?); (b) occlusion of the vessels by deposited platelets, agglutinated red blood cells and fibrin; (c) necrosis of vessel walls and regional trophoblast and, finally, (d) rupture of these structures and hemorrhage of fetal blood into the adjacent maternal sinuses.

Brindeau and Nattan-Larrier,[1] in 1908, reported the constant finding of vascular thrombi in the decidua and villi in the normal placenta, especially toward term. In addition to these changes, often associated with infarct formation in the normal placenta, they reported the occurrence of numerous small and large fetal hemorrhages in the placenta of the eclamptic patient.

In places, gaps in the walls of the blood vessels and regional epithelial lining of villi, were observed, with unquestionable communication of the fetal and maternal circulations. Fetal red blood cells continuing through such orifices into the maternal sinuses were readily recognized.

The process of the formation of placental tissue by organization of regional blood clots is similar to that which occurs postnatally in other organs, notably in the ovary. Novak,[8] in 1917, called attention to the ovarian origin of some abdominal hemorrhages. Since then, bleeding into the peritoneal cavity following ovulation or rupture of a corpus hemorrhagicum or corpus luteum cyst has been noted not infrequently clinically and at operations for acute appendicitis and for ruptured ectopic pregnancy (McSweeny and Wood,[7] 1940). As early as 1899, Gersuny[2] related the formation of some lower abdominal and pelvic adhesions to the organization of fibrin masses after hemorrhage into the peritoneal cavity following ovulation and not to previous inflammation. Some of these involved the surface of the ovary.

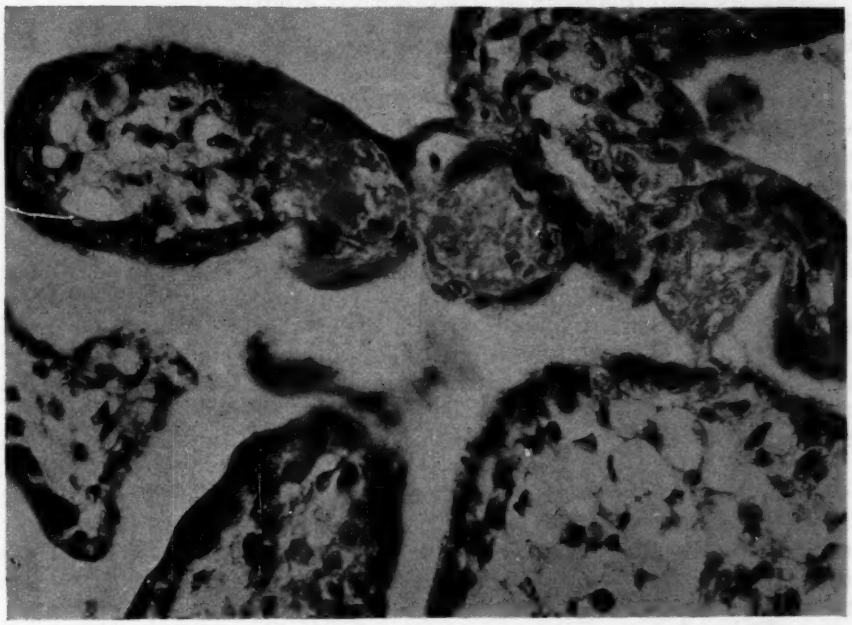


Fig. 1.—Placenta of 3½ months' pregnancy. Magnification about 400× (upper center). Occlusion of vessels of villi by agglutinated red blood cells and fibrin.

During the course of the routine gross and microscopic examination of specimens removed at over 61,000 operations at Mount Sinai Hospital, Cleveland, during the past 26 years, scores of ovaries have been observed with one or more recent blood clots adherent to the surface. Other specimens have shown ingrowth into adherent blood clots of fibrocapillary tissue springing from the regional tunica albuginea and lining of the surfaces of the clots by germinal epithelium extending from that of the ovary regional to them. The new fibrocapillary tissue is finally replaced by, or develops into, a denser fibrous tissue indistinguishable from the regional residual ovarian tunica albuginea. Not infrequently there are associated small cystlike clefts lined by germinal epithelium. In some cases, the size of the organ is increased one or more times, over a period of years, by the complete organization of blood clots adhering to the surface after ovulation.

Placenta of Very Early Normal Pregnancy (2 Weeks to 2 Months)

Microscopic examination of sections of an intact and well-fixed gestation sac of about two weeks, 3½ mm. in diameter, in situ in utero, and sections of a second specimen of about three weeks, 17 mm. by 6 mm. in dimension, also in situ in utero, shows independent trunks and villi regional to one another and everywhere intact. The sections show clearly the vigorous dissection of the maternal decidua by large syncytial cells adjoining one another or spearheading the tips of growing villi. The sections, furthermore, show invading syncytial cells opening up blood vessels of the regional maternal tissues and the dissection of the decidua into many irregular masses, some of which, in one plane, have a considerable resemblance to the fetal villi. The tips of villi are firmly bound by syncytial cells to the ends and sides of these structures (fastening villi). Examination of the villi of a placenta of about one and one-half months shows no appreciable abnormality of epithelium or of stroma.

Placenta of Two to Four Months

In a series of 114 placentas of two to four months, the majority of villi at two months measure about 150 to 200 microns in thickness, at three months about 300 microns and at four months about 400 microns. Syncytial and Langhans layers are both present until toward the end of this period, when Langhans cells are fewer than previously. The fibrous tissue core at four months is decidedly thicker than previously, but the cells are still of early fibroblastic type. Blood vessels appear most prominently in the placentas of the third month, many lying just below the epithelium, and these are filled with nucleated red blood cells. The vessels in small and large trunks, especially the latter, are identifiable as arteries, veins, and capillaries. In some of the sections, small hemorrhages within occasional villi are observed and Hofbauer cells are seen fairly frequently, especially in placentas of about four months. Some contain altered red blood cells. Early in the period, the syncytial cells vary in size and are very large at the tips of some of the villi. In the placentas of the second month, occasional villi are observed which show degenerative changes of the epithelium, especially of the syncytium as follows: vacuoles of varying size, shrunken cells, pyknotic or eosin-stained nuclei, cytoplasm granular and intensely stained. As early as the third month, occasional villi are observed loosely adherent to each other by masses of degenerated epithelium. More rarely occlusion of some blood vessels by agglutinated red blood cells and fibrin is observable (Fig. 1).

Placenta of Four to Six Months

Microscopic examination of 23 placentas in this period shows villi progressively thinner than previously (300-250 microns in diameter) and the stroma more compact. The Langhans cells are few in number or completely absent and syncytial cells are thinner than at earlier periods. Villi with adherent masses of degenerated epithelium are few, but many villi and trunks, especially in the placentas of the fifth and sixth months, are observed with some parts of the surface epithelium absent and the stroma in these areas covered by blood clot. Many of the clots extend from villus or trunk through a broken surface into the adjacent maternal sinuses and about neighboring villi or trunks. In addition to these changes and in places associated with them, peripheral blood vessels of some villi and trunks are occluded by agglutinated red blood cells and fibrin and there is necrosis of regional vessel walls and surface epithelium. At times, especially with involvement of larger vessels of small trunks, the hemorrhages are larger and the resultant clots are

Fig. 2.

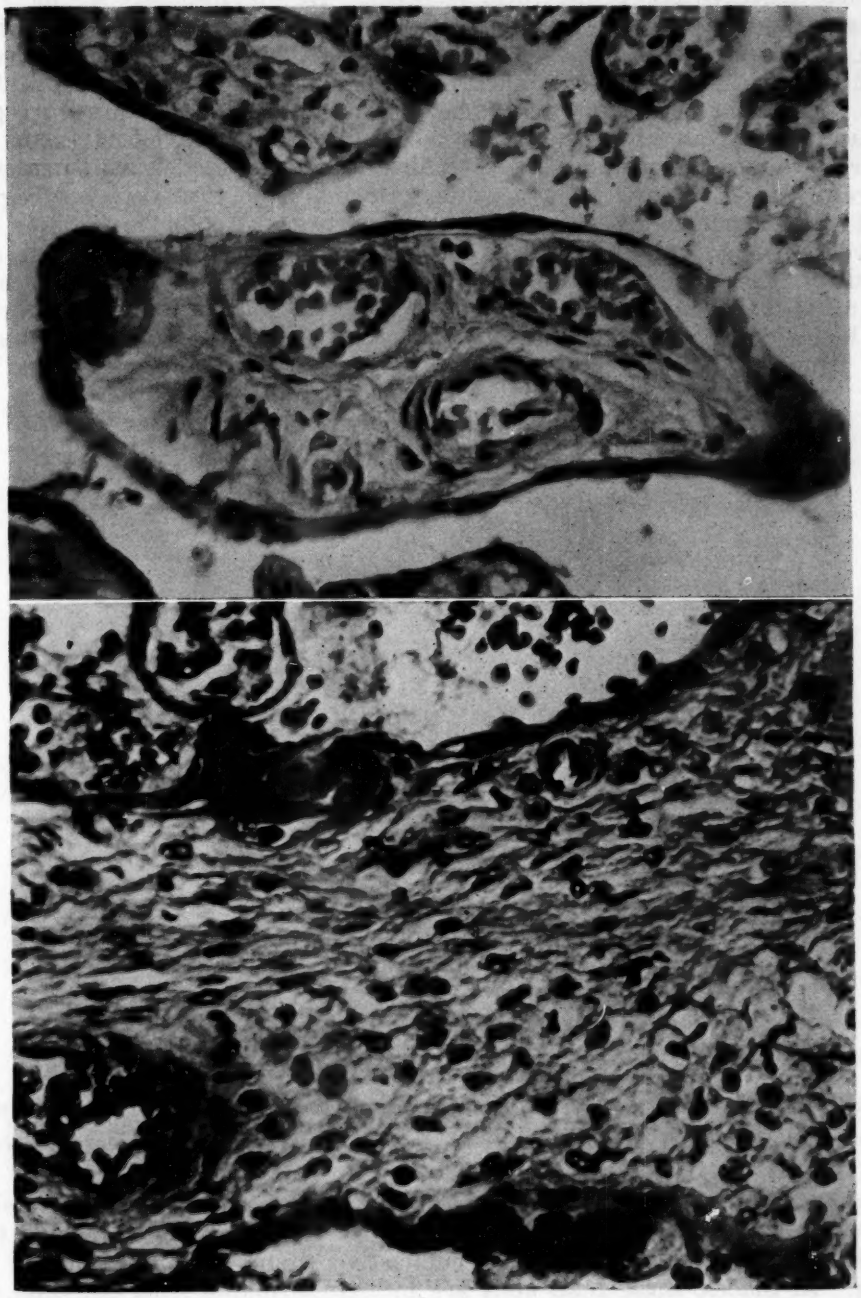


Fig. 3.

Fig. 2.—Placenta of full-term pregnancy. Magnification about 400× (left middle). Occlusion of a vessel of a villus by agglutinated red blood cells and fibrin. Necrosis of vascular wall and regional surface epithelium.

Fig. 3.—Placenta of full-term pregnancy. Magnification about 400× (upper left and upper central). Occlusion of blood vessel of small trunk by agglutinated red blood cells and fibrin.

observed intimately encircling a considerable number of villi, the latter showing degenerative or necrotic changes. In the majority of clots, the cellular elements are no longer visible and the masses appear as cylinders of fibrin. In a few placentas, however, very recent blood clots are observed in which the red blood cells, enmeshed in the fibrin, are intact and easily identifiable. In the areas of very recent hemorrhage, the blood clots are irregular in shape. Subsequently they appear molded to shapes resembling shorter or longer branches of villi or small trunks. These molded fibrin masses are apparently soon covered by syncytium growing from that covering regional intact villi or trunks. Later, apparently, ingrowth of connective tissue from involved villi or trunks occurs and eventually complete fibrovascular anastomosis of these structures results. Although it is possible to recognize newly forming villuslike and trunklike structures on the scaffolding of the fibrin of fetal blood clots, it is impossible to tell recently completely organized structures from branches of residual villi or portions of residual trunks.

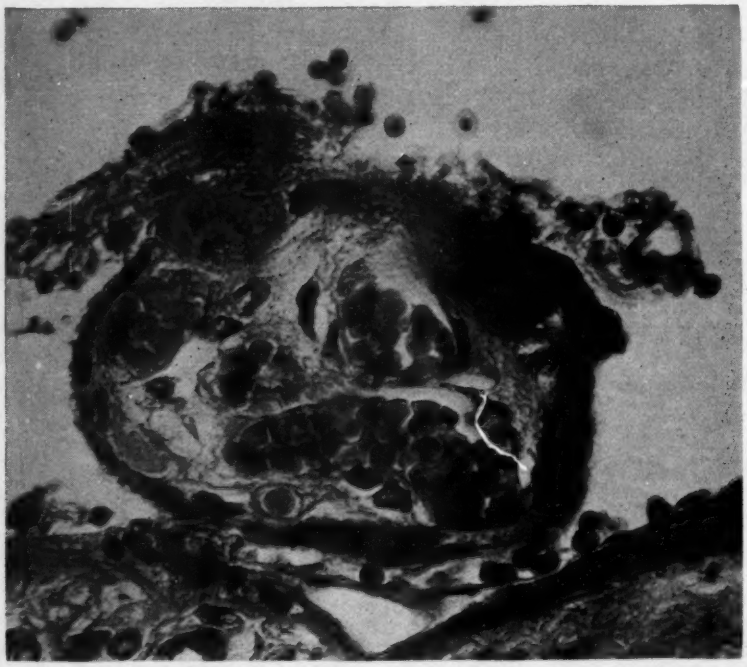


Fig. 4.—Placenta of full-term pregnancy. Magnification about 700× (upper and middle central and right and upper central). Occlusion of vessels of villi by agglutinated red blood cells and fibrin. Necrosis of walls of vessels and regional surface epithelium with rupture.

In some placentas at this time, many of the masses of fibrin, progressively replaced by connective tissue ingrowth, show the newly formed cells to be decidedly larger than the residual connective tissue cells from which they spring. In places, these fetal cells are indistinguishable from decidual cells. It has been observed in our surgical material that not infrequently a distant decidual reaction occurs in cases of uterine pregnancy and that recently formed fibrous tags that have replaced blood clots adherent to the surface of the ovary, omentum, appendix, etc., show connective tissue cells transformed into typical decidual cells. The picture in the placentas of this and later periods suggests that some newly formed fetal connective tissue cells, growing into fetal blood clots in intervillous spaces, exposed to the progesterone in the

Fig. 5.

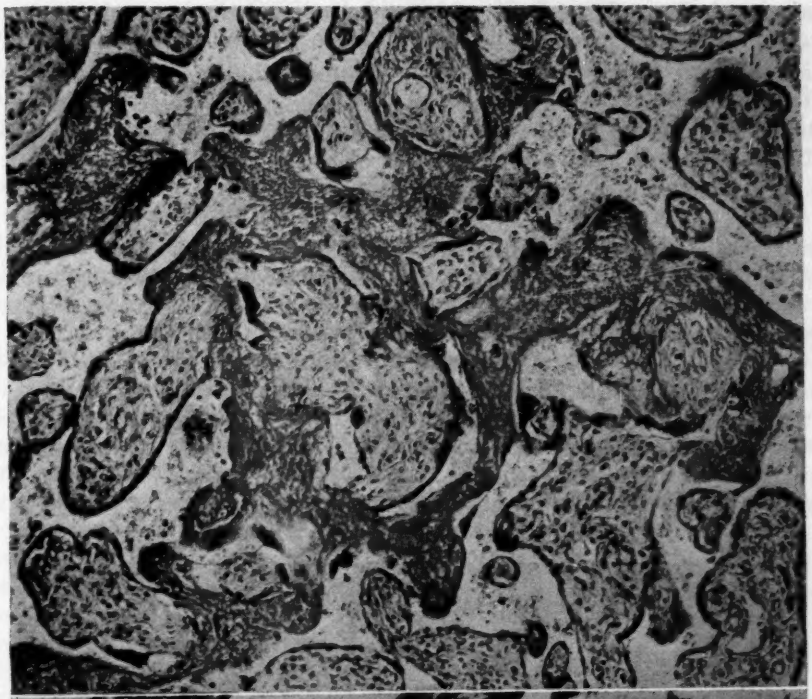


Fig. 6.

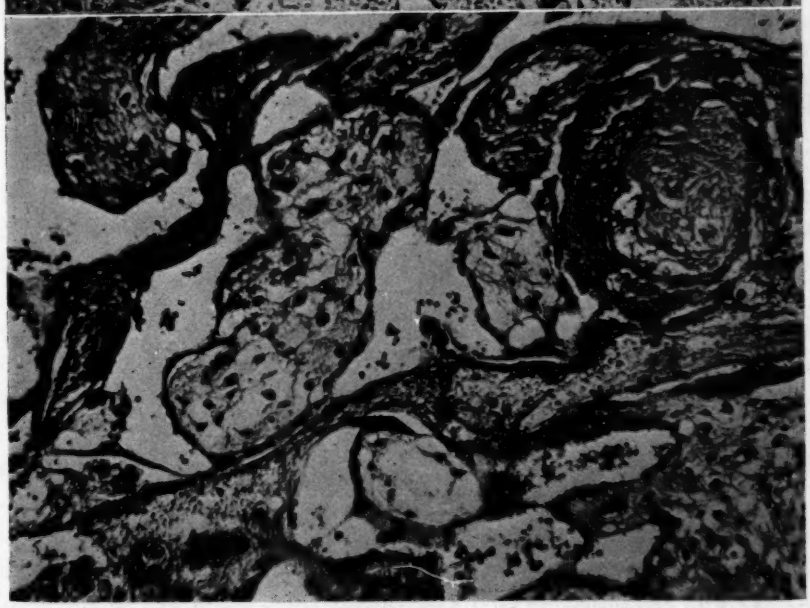


Fig. 5.*—Placenta of 8½ months' pregnancy, case of erythroblastosis fetalis. Magnification about 100×. Numerous fibrin masses, remains of fetal hemorrhages, binding villi together. Beginning organization by syncytial proliferation.

Fig. 6.*—Placenta of 8½ months' pregnancy, case of erythroblastosis fetalis. Magnification about 200×. Placental tissue formation by organization of fetal blood clots. Note villus-like structure (near left upper corner), showing organization of mass of fibrin by syncytium and early connective tissue proliferation; to the right of this, bat-shaped fibrin mass, showing beginning organization by syncytial proliferation; and to the right of this a villuslike structure, organized fibrin mass of old fetal hemorrhage almost indistinguishable from residual villus in lower right-hand corner.

---

*Figs. 5 and 6 republished by permission of Dr. William Dameshek, Editor of *Blood*, and Grune and Stratton, Inc., Publishers.

maternal circulation, respond to it just as some adult endometrial stromal cells and newly formed maternal connective tissue cells, elsewhere than in the uterus, do in uterine pregnancy. It is difficult to distinguish some of these areas of organizing fetal blood clots in the placenta from islands of maternal decidual cells. These cell islands are generally considered to be composed of Langhans cells.

Placenta of Six to Eight Months

Microscopic observation of five placentas of this period shows villi somewhat thinner than previously (about 250-150 microns in diameter). The blood vessels are more numerous and the stroma more compact than before. The syncytial cells are thinner than they were earlier and there is less fibrous stroma between them and the vascular endothelium. As in the placentas of the fifth and sixth months, areas of vascular and epithelial damage of villi and trunks are present. Similarly, recent and older blood clots of fetal hemorrhage into intervillous spaces are observable. Many of the clots continue from damaged villus or trunk to regional villus, villi, or trunk. Likewise, the later changes of organization noted in placentas of the previous period are seen.

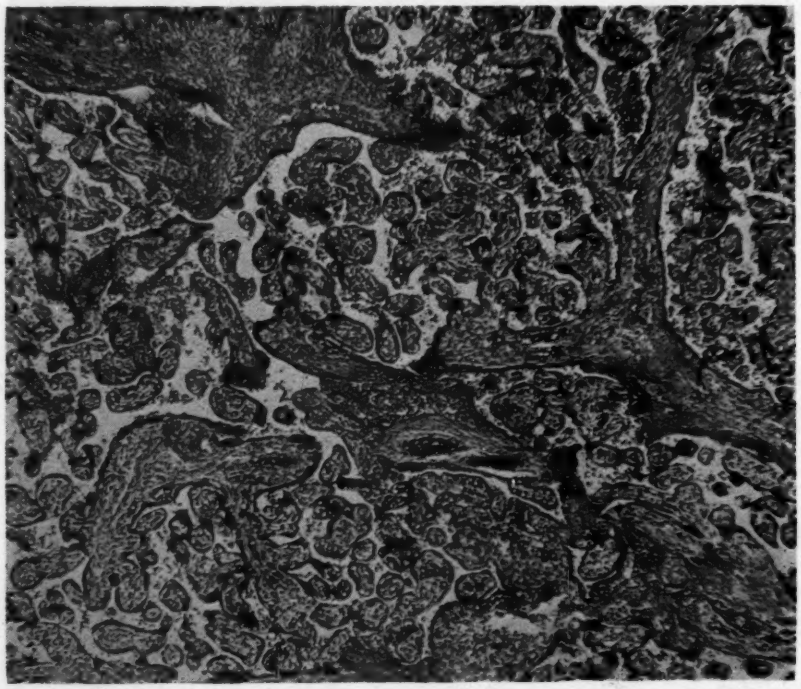


Fig. 7.—Placenta of full-term pregnancy. Magnification about 400×. Rupture of many villi and trunks with blood clots of fetal hemorrhages binding villi and trunks to each other and showing various stages of organization (resemblance of placenta to a sponge).

As before, complete anastomosis of villus with villus, villus with trunk, and trunk with trunk is observed, and somewhat more frequently than earlier. Areas of organizing fetal clots resembling islands of maternal decidual cells are also seen. These areas vary from a few hundred microns to over 4 mm. in diameter. Some show ingrowth of blood vessels, others show degenerative or necrotic change of some of the large cells.

Placenta of Eight to Ten Months

Microscopic observation of 198 placentas of this terminal period show the villi to be still thinner than previously (about 150-75 microns) and with blood vessels still more numerous and more prominent than before. The fibrous stroma between syncytium and vascular endothelium is comparatively small in amount and compact. As in placentas of the previous period, areas of vascular occlusion, necrosis of walls and regional epithelium, with rupture, and hemorrhage of fetal blood into the adjacent intervillous spaces are observed (Figs. 2, 3, and 4). Numerous villi and trunks show adhesions to each other by recent and old clots and many show partial to complete organization with anastomosis of villus to villus, villus to trunk, and trunk to trunk (Figs. 5 and 6). The resemblance of the placenta at this time, to a sponge rather than to a thicket of miniature trees, suggested earlier, is striking (Fig. 7). Islands of fetal connective tissue cells resembling decidual cells are present, some show areas of degeneration and necrosis and some show calcium deposits. Other well-known changes of maturation and senescence of the placenta are clearly visible in the terminal period.

The changes in the placenta in the last half of normal pregnancy, described above, are similar to those observed in the placentas in cases of erythroblastosis fetalis.[5] In addition, in the placentas in 8 of the 15 cases of this disease, the villi show characteristic thickening of surface epithelium and of stroma. Many villi, at or near term, in cases of erythroblastosis, show a double layer of epithelium resembling that of villi of the first few months of normal pregnancy. In the placenta in cases of erythroblastosis, the changes are probably a response to constant exposure to the harmful fetal red blood cell antibody of the maternal blood. The possibility is suggested that the thick double epithelial layer of villi in the first few months of normal pregnancy is required to insure a selectivity of exchange greater than is necessary later on.

Comment

Microscopic observation of 117 human placentas of normal pregnancy, from 2 weeks to 4 months, shows villi and trunks completely independent of one another, and, almost without exception, wholly intact. In 213 placentas of the last half of normal pregnancy, however, breaks in the surface of numerous villi and trunks are observable, the underlying stroma covered by fetal blood or recent or old fetal blood clots. Many of the clots extend in all directions from their source. They bind one or more villi or one or more trunks to each other. In many places, the cellular elements of the clots are no longer present and masses of fibrin only remain. In places these are covered by syncytium extending from intact portions of regional villi or trunks. In places, connective tissue from regional villi or trunks is observable extending into the fibrin cores. In some areas, completely organized structures, almost or entirely indistinguishable from similar residual villi and trunks, are present. These observations indicate the capacity of fetal tissues to organize blood clots as adult tissues do. They also support the contention of Stieve that many of the villi and trunks are anastomosed to each other in the second half of pregnancy and that, at this time, the organ resembles a sponge and not a thicket of miniature trees.

It has been generally accepted that the fibrin masses in the placenta, in intervillous spaces and adherent to fetal structures, are entirely of maternal

origin. Evidence that the fibrin masses are of fetal origin is especially convincing in 2 of 13 placentas of fatal cases of erythroblastosis fetalis.[6] In one of these 2 cases, the baby, of 8½ months' pregnancy, lived 33 minutes, and the other, of 7½ months' pregnancy, lived 25 minutes. Numerous sections of these placentas show clearly numerous breaks in the surface of villi and trunks. Covering the denuded areas, in places, there is intact fetal blood, and many of the red blood cells are nucleated. Elsewhere, very recent and recent blood clots containing intact and degenerating nucleated fetal red blood cells are observable. These latter are apparently the remains of hemorrhages that occurred shortly before expulsion. These two placentas also show, in many places, binding of villi and trunks to each other by fetal blood clots in various stages of organization.

Microscopic study of 213 placentas in the second half of normal pregnancy indicates that the changes described above result as follows: (1) damage to the small peripheral blood vessels and regional trophoblast of villi and trunks (by excretory products?); (2) occlusion of the injured vessels by platelets, agglutinated red blood cells, and fibrin; (3) necrosis of vessel walls and of regional trophoblast; and (4) rupture of these structures and hemorrhage of fetal blood into adjacent maternal sinuses.

The process of the formation of fetal placental tissue by organization of fetal blood clots, described above, is similar to that of the formation of ovarian tunica albuginea in adults, from blood clots adhering to the surface of the ovary after ovulation.

Summary

The placenta in the first trimester of pregnancy is composed of separate and independent trunks and branching villi resembling a miniature thicket of trees. Later, and pronounced in the last half of pregnancy, newly formed placental tissue results from the organization of fibrin masses, the remains of multiple fetal hemorrhages from villi and trunks into regional intervillous sinuses. Many of the villi and trunks in the last half of pregnancy, consequently, are firmly adherent to one another and the organ resembles a sponge.

I wish to acknowledge, with thanks, the helpful suggestions of Professor Leslie B. Arey of Northwestern University relating to the manuscript.

References

1. Brindeau, A., et Nattan-Larrier, L.: Obstetrique 13: 1, 1908.
2. Gersuny, R.: Wien. klin. Wchnschr. 12: 601, 1899.
3. Grosser, Otto: Ztschr. f. Anat. u Entwcklngsgesch. 76: 304, 1925.
4. Kalima, T.: Ueber den sog. Weiszen Infarct der Placenta, Berlin, 1912, S. Karger.
5. Kline, B. S.: Am. J. Obst. & Gynec. 53: 226, 1948.
6. Kline, B. S.: Blood 4: 1249, 1949.
7. McSweeney, D. J., and Wood, F. O.: New England J. Med. 222: 174, 1940.
8. Novak, E.: J. A. M. A. 68: 1160, 1917.
9. Sidall, R. S., and Hartman, F. W.: Am. J. Obst. & Gynec. 12: 683, 1926.
10. Stieve, H.: Zentralbl. f. Gynäk. 59: 434, 1935.
11. Stieve, H.: Arch. f. Gynäk. 174: 452, 1942.
12. Wislocki, G. B., and Bennett, H. S.: Am. J. Anat. 73: 335, 1943.

THE DIAGONAL CONJUGATE

D. FRANK KALTREIDER, M.D., BALTIMORE, MD.

(From the Department of Obstetrics, University of Maryland Medical School)

THE importance of the relationship between the true conjugate (C.V.) and the diagonal conjugate (C.D.) was first demonstrated by Smellie in 1752, almost two hundred years ago. He stated that the C.D. was 1.5 cm. to 2.0 cm. longer than the C.V. Most obstetricians, since then, have accepted this relationship without question. In recent years the two terms, true conjugate (C.V.) and obstetrical conjugate (C.O.), have become synonymous, and similarly obstetricians usually think in terms of the C.O. when discussing Smellie's rule. Jacobs[1, 2, 3] has written several articles delineating the discrepancies in this rule as has Dippel,[4] who is measuring the diagonal conjugate and obstetrical conjugate in fifty-four cases by x-ray noted the greatest difference to be 3.1 cm., the shortest difference 0.1 cm. and the mean to be 1.3 cm. Jacobs, using the true conjugate (C.V.) rather than the C.O., said he found that 8 per cent of cases fell in the group in which the C.V. was 1.5 to 2.0 cm. shorter than the C.D.; and in 89.5 per cent the difference was less than 1.5 cm. The recognition of this fact has finally infiltrated into modern teaching in that in the tenth edition of Williams' *Obstetrics,*[5] recently revised by Eastman, Dippel's and Jacobs' work has been cited.

Material

During the period July 1, 1947, to July 1, 1950, 1,169 patients were measured by x-ray pelvimetry and these x-rays were studied at the University Hospital. Since some of these patients were delivered in other hospitals, thirty-six delivery records could not be obtained, so that only 1,133 x-rays were studied. There were in this series 542 white and 591 Negro patients. The age range was from below 15 to over 40, the vast majority being between 16 and 30 years of age. Eight hundred sixty-two patients were primigravidas, 194 para i, and the remainder of a higher parity. These x-rays have been studied from various angles, but in this presentation our considerations will be confined to the diagonal conjugate.

The Relationship of the X-ray C.O. to the X-ray C.D.

Five hundred seventy-two x-rays from this group were studied to determine the relationship of the x-ray C.O. to the x-ray C.D. The C.O. was read on the x-ray film as the shortest distance between the upper portion of the symphysis and the most prominent part of the upper sacrum. The posterior end point varied considerably, and is demonstrated in Figs. 1, 2, and 3. The top of the sacrum was most frequently the closest point to the symphysis (Fig. 1), while the middle of the first sacral segment was less commonly found

to be the posterior end point (Fig. 2), and occasionally it was the fifth lumbar vertebra (Fig. 3). The anterior end point of the C.O. is demonstrated clearly in these figures while the anterior end point of the C.D. is the most inferior extremity of the symphysis pubis. The posterior end point of the C.D. was the same as was used in the C.O.

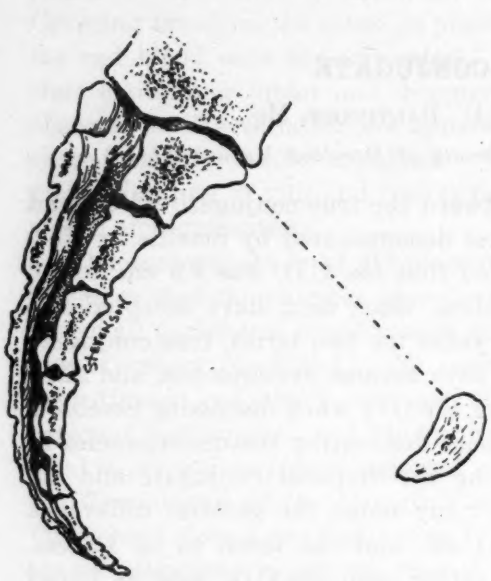


Fig. 1.

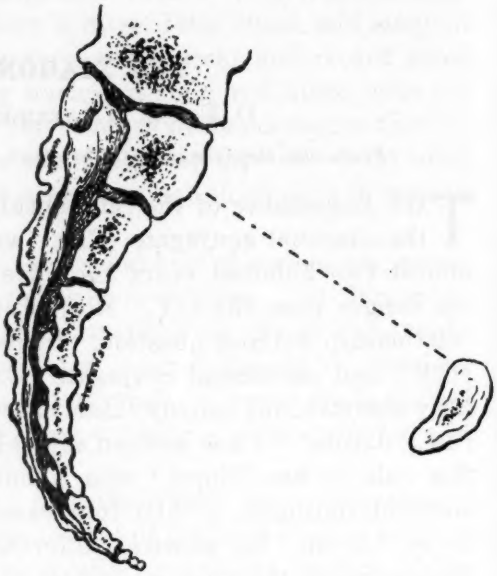


Fig. 2.

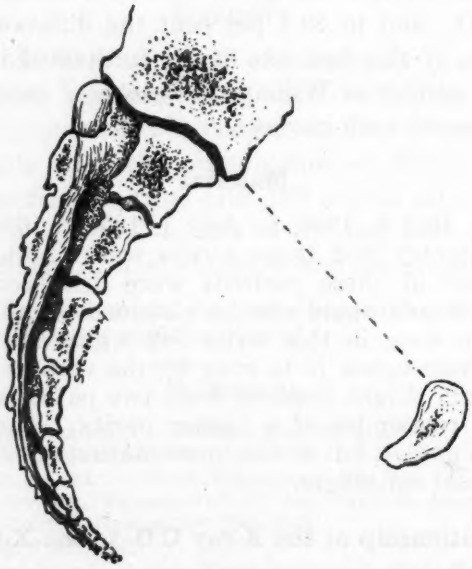


Fig. 3.

The results of the differences between the C.D. and the C.O., using these end points, are shown in Fig. 4. The largest variation is 2.5 cm., and the shortest variation is 0.2 cm. The mean is 1.19 cm., the median 1.30 cm. and the mode 1.20 cm. Approximately 21 per cent of the readings fell in the group in which there was 1.5 to 2.0 cm. difference. Less than 1 per cent of these

readings were greater than the usually accepted difference and about 88 per cent were less. One could interpret from these results, which closely follow those of Dippel and Jacobs, that one would get into difficulty in less than 1 per cent of cases by using the x-ray C.D. as an index to inlet contraction. This is probably true. However, the x-ray C.D. is practically never read. The clinical C.D. is the measurement usually ascertained in the clinical evaluation of the inlet. Let us see how accurate the clinical C.D. is.

How Accurate Is the Clinical C.D.?

The next step in this study consisted of evaluating the clinical C.D. with the x-ray C.D. This was based on the use of 611 cases in which the clinical C.D. was measured and the x-ray C.D. read. These patients have been divided into two groups. The first group of 136 patients was examined clinically by the resident obstetrical staff at the University Hospital and not checked by a visiting obstetrician. The second group consisted of 475 patients, including house cases checked by the visiting obstetricians and private patients of the visiting obstetricians. Tables I and II give the actual readings of the x-ray C.D. in 0.2 cm. levels compared with the clinical readings in 0.5 cm. levels.

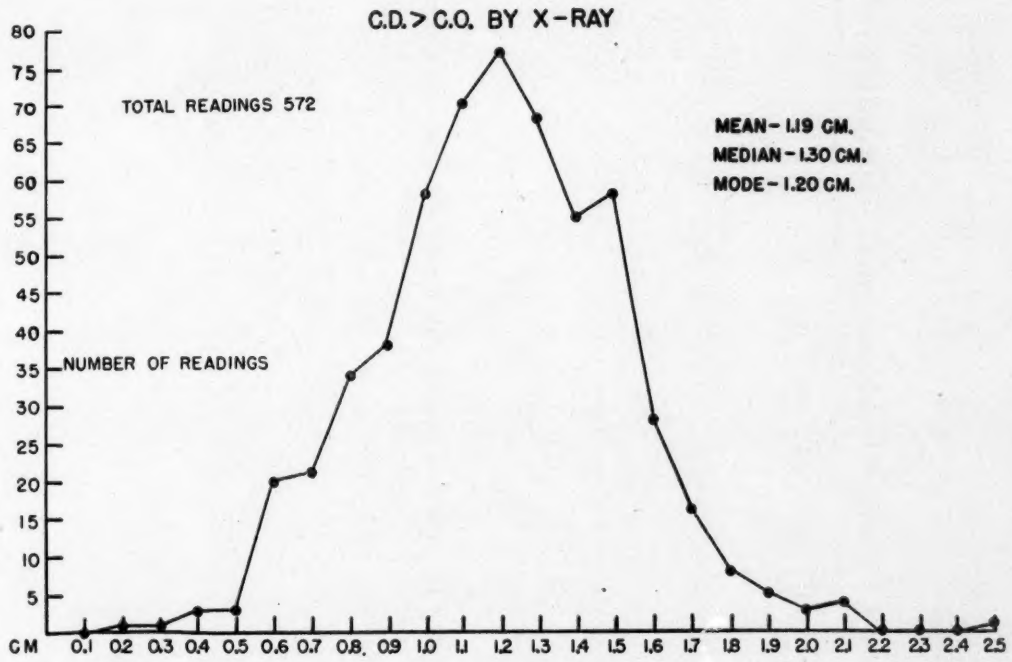


Fig. 4.

It is quite obvious that the clinical measurement of the C.D. is grossly inaccurate. This does not mean, however, that it is of no value. Since a clinical C.D. of 11.5 cm. is usually considered borderline, the two groups were analyzed to see what percentage of those patients in whom the clinical C.D. was over 11.5 cm. had an actual x-ray C.D. of over 11.5 cm.; and correspondingly, the group with the clinical C.D. of under 11.5 cm. was considered the same way. In the latter group about 40 per cent of the x-ray C.D.'s were actually under 11.5 cm., while in the patients in whom the clinical C.D. measured over

TABLE I. RESIDENT OBSTETRICAL STAFF. CLINICAL C.D.'S COMPARED WITH X-RAY C.D.'S

CLINICAL C.D.	9.8	10.0	10.2	10.4	10.6	10.8	11.0	11.2	11.4	11.6	11.8	12.0	12.2	12.4	12.6	12.8	13.0 AND OVER
9.1- 9.5	1																
10.1-10.5	1																
10.6-11.0											1		1	1			
11.1-11.5				2		2		1	1	1	4	1			1		1
11.6-12.0									3	1	1	1	2	2	2	3	5
12.1-12.5						2		1	1	4	4	2	2	4	1	3	7
12.6-13.0													2			1	5
Not reached							1	1	1	6	5	1		7	2	7	27

TABLE II. VISITING OBSTETRICAL STAFF. CLINICAL C.D.'S COMPARED WITH X-RAY C.D.'S

CLINICAL C.D.	9.8	10.0	10.2	10.4	10.6	10.8	11.0	11.2	11.4	11.6	11.8	12.0	12.2	12.4	12.6	12.8	13.0 AND OVER
8.6- 9.0	1								1								
9.1- 9.5		1				1			1								
9.6-10.0	1		1	1	3	1		1	1	3	1		1	1		1	
10.1-10.5			1		3	4		8	7	2	3	3	2		1		
10.6-11.0					3	2		8	9	9	15	4	3	6		1	
11.1-11.5						1	3	2	5	8	12	6	4	9	4	7	9
11.6-12.0					1	1	3	5	6	4	8	4	7	2	8	7	26
12.1-12.5						1			3	1	4	3		4	2	2	11
12.6-13.0												1		1	1	1	6
Not reached	1						2	2	3		8	9	6	12	21	18	82

11.5 cm. the actual x-ray C.D.'s in slightly over 90 per cent of the cases measured over 11.5 cm. Unfortunately, in about 9 per cent of the cases in which the clinical C.D. was over 11.5 cm. the actual x-ray C.D. was less than 11.5 cm. It may be noted to the detriment of our egos that the evaluation of the C.D. by the postgraduate student (the resident obstetrical house staff) is as accurate or rather as inaccurate as that of the visiting obstetricians.

It is assumed that the C.D. can be measured more readily when the patient is a multigravida. One hundred forty-two multigravidas were analyzed with this idea in mind. In the 79 multigravidas in whom the clinical C.D. was measured at greater than 11.5 cm., over 12 per cent of the patients had an x-ray C.D. of under 11.5 cm., not quite as good a record as in the entire group. The lowest C.D. by x-ray was 10.6 cm. In the 63 multigravidas in whom the clinical C.D. was below the critical level, the x-ray C.D. was also below in 47 per cent of cases; a slightly better record than in the combined groups, but certainly in either case not sufficient to make any major difference, whether the patient was a primigravida or a multigravida.

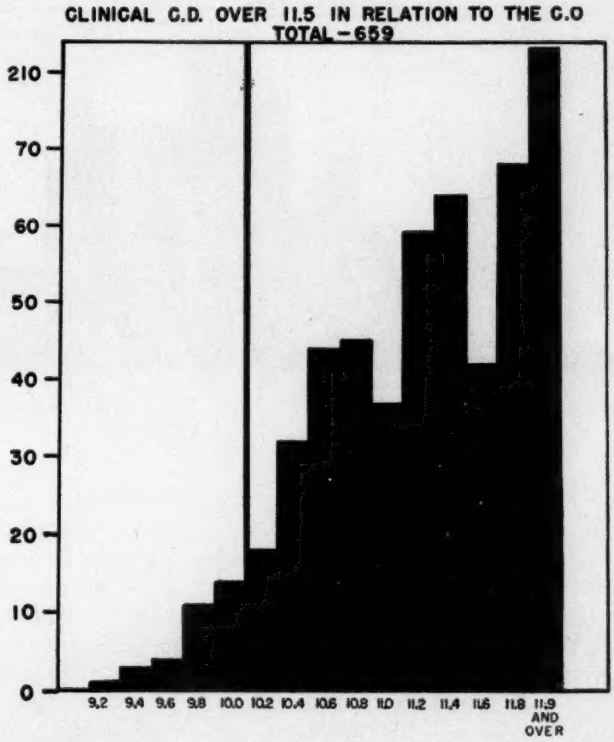


Fig. 5.

Relation of Clinical C.D. and X-ray C.O.

Of more importance is the relationship of the clinical C.D. to the actual C.O. Eastman[5] states, "If this measurement (C.D.) is greater than 11.5 cm. or if the promontory of the sacrum cannot be reached at all, it is justifiable to assume that the pelvic inlet is of adequate size for childbirth. In sixty-one consecutive cases in which the diagonal measurement exceeded 11.5 cm. in our clinic, there was not a single instance in which the obstetrical conjugate fell below 10.0 cm." It is assumed that a C.O. of 10.0 cm. is the border line between a normal and contracted pelvis. Six hundred fifty-five pelves were

analyzed from this viewpoint. When the clinical C.D. was over 11.5 cm., the C.O. varied from 9.2 cm. to over 11.9 cm. (Fig. 5 demonstrates this variation). Note that 33 patients out of 655 or one in twenty of those with a clinical C.D. of 11.5 or more had a C.O. of 10.0 cm. or less. This is what happened to those 33 patients. Fifteen had spontaneous or control low forceps deliveries. Three patients had difficult midforceps deliveries with one fetal death from intracranial hemorrhage. There were 15 sections, 6 elective and 9 following labor. Of the elective sections 2 were for previous sections, the indication in the previous pregnancies being inlet contraction after labor. In the 9 sections with labor, one was done for uterine inertia and 8 for obstructed labor. Including the patient with fetal death from intracranial hemorrhage, there were 11 cases of obstructed labor. One-third of these patients needed sections because of contracted pelvis. Not too good an outlook when one is lulled into security by a C.D. of over 11.5 cm.

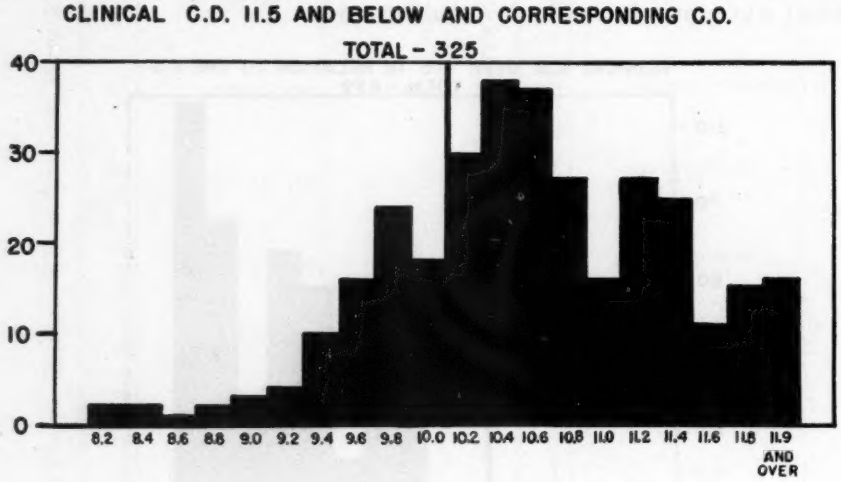


Fig. 6.

On the other hand, as has been suggested by Dippel's work and corroborated here, since there can be considerable variation in the difference between the C.D. and C.O. and if the clinical C.D. is below 11.5 cm., it does not necessarily mean that pelvic contraction exists, and therefore that cesarean section is indicated for inlet disproportion. Nothing can be further from the truth. In Fig. 6 is shown the actual C.O. measurements by x-ray when the clinical measurements of the C.D. were below 11.5 cm. Note that in 242 out of 324 cases or in three out of every four patients in whom the C.D. was measured at 11.5 cm. or less, the C.O. was greater than 10.0 cm. A small clinical diagonal conjugate does not necessarily mean a small pelvis.

Clinical Results With the Clinical C.D.

Nine hundred eighty-four cases were analyzed from the viewpoint of the clinical diagonal conjugate above and below 11.5 cm. and the clinical outcome. Three hundred twenty-five patients fell in the group below 11.5 cm. and 659 fell in the group above 11.5 cm. Figs. 7 and 8 and Tables III and IV demonstrate these results briefly. The definitions need explanation. Easy deliveries were those consummated spontaneously or with control outlet forceps. Difficult deliveries were those forceps deliveries in which the amount of traction necessary for delivery was deemed excessive. It is admitted that this

is vague, but until the difference between excessive and normal forceps traction can be determined, it is the best one can do. Sections with labor were those in which labor started and progressed to at least 4 cm. dilatation and section was then done for uterine inertia or obstructed labor. Obstructed labor consisted of labor with pains closer than five minutes apart, sustained for a minimum of three hours, with increasing cervical dilatation, and with a floating or dipping head either clinically or by x-ray evidence, if inlet obstruction occurred, and full dilatation of the cervix with the head below the spines and no progress after three to seven hours of full dilatation, if midplane obstruction occurred. Uterine inertia was desultory labor regardless of whether the head was in the pelvis or floating.

TABLE III. CLINICAL RESULTS, CLINICAL C.D. 11.5 CM. AND UNDER

SECTIONS—67					
Without Labor.—		43	With Labor.—		24
Elective	30		Obstructed labor	17	
Toxemia	2		Inlet	16	
Hemorrhage	2		Midplane	1	
Other	1		Inertia	7	
Previous sections	8				
Cephalopelvic disproportion	5				
Elective	2				
Elderly 0000	1				

FETAL DEATHS AND CAUSES

TYPE OF DELIVERY	TOTAL DELIVERIES	NUMBER OF FETAL DEATHS	ANOXIA	INTRACRANIAL HEMORRHAGE
Easy	239	2	1	1
Difficult	18	2	0	2
Sections	67	1	1	0

TABLE IV. CLINICAL RESULTS, CLINICAL C.D. OVER 11.5 CM.

SECTIONS—97					
Without Labor.—		52	With Labor.—		45
Elective	23		Obstructed	29	
Toxemia	5		Inlet	27	
Hemorrhage	4		Midplane	2	
Other	6		Inertia	16	
Previous sections	14				
Cephalopelvic disproportion	10				
Toxemia	2				
Hemorrhage	1				
Elderly 0000	1				

FETAL DEATHS AND CAUSES

TYPE OF DELIVERY	NO. OF DELIVERIES	NO. OF FETAL DEATHS	ANOXIA	INTRACRANIAL HEMORRHAGE	ANOMALY	INFECTION	INERTIA	PELVIS
Easy	518	15	4	2	4	1	3	1
Difficult	44	4	0	3	1	0	0	0
Sections	97	2	1	1	0	0	0	0

In order to arrive at the percentage of inlet obstructions in the two groups the cases of elective section (except for previous sections done for cephalopelvic disproportion), and sections done for uterine inertia must be eliminated. Patients with sections for midplane obstruction are not included in obstructed labor, since the inlet was surpassed. In the C.D. group below 11.5 cm. this leaves 278 patients with 21 obstructed labors. We feel that since 3 of the fetal deaths were due to intracranial hemorrhage these 3 cases should be considered in the group with obstructed labor, since they should have had cesarean section. The rate, then, of obstructed labor (24 cases) in the group with a C.D. of 11.5 cm. or less was 8.6 per cent.

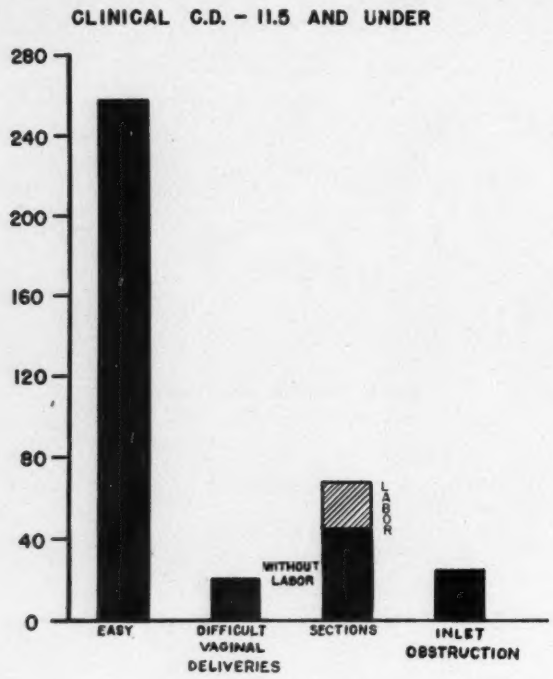


Fig. 7.

If the group in which the C.D. was over 11.5 cm. is treated similarly, there remain 599 patients. Of these, 37 patients had obstructed labor at the inlet. Six babies that were delivered vaginally should also be included since five died of intracranial hemorrhage and there was one craniotomy. The rate of obstructed labor (43 cases) in this group was 7.2 per cent.

The difference of only 1.4 per cent between the two groups is more apparent than real. It may be argued that many of the cases of so-called obstructed labor were cases of uterine inertia. This may be true. However, many of these were checked with sterile pelvic examinations or with lateral x-ray films late in labor, which showed the head floating or only dipping in the pelvis and the biparietal diameter well above the inlet and in many cases considerable fetal cephalic molding. Obviously, some of these were excessively large babies, as witness one weighing over 5,500 grams who was delivered by cesarean section, and the C.D. was not reached. But an excessive-sized infant, generally, was not a factor. One must remember that this is a highly selective group of patients. Table V illustrates the various indica-

tions in both groups for doing pelvimetry. It is quite obvious that "suspect" pelvis played a much more important role in the lower C.D. group, while x-rays taken electively played an important role in the higher C.D. group. Without much doubt most of the patients with the C.D. below 11.5 cm. had x-ray pelvimetry, while a comparatively small percentage of the patients with a C.D. of over 11.5 cm. had pelvimetry. If pelvimetry were done in all patients, the percentage of obstructed labors in patients with C.D.'s of over 11.5 cm. would drop precipitously. Because of suspected midplane and outlet contractions, x-rays were more frequently obtained in the higher C.D. group.

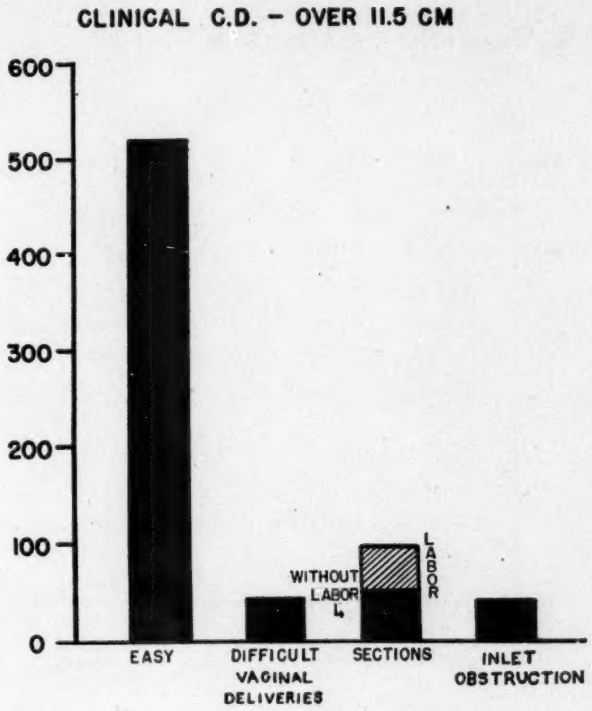


Fig. 8.

TABLE V. REASONS FOR PELVIMETRY

REASONS	C.D. OVER 11.5	C.D. 11.5 AND UNDER
Elective	172	11
Suspect pelvis	263	254
Abnormal presentation	61	3
Previous difficult delivery	33	18
Floating head at term	38	6
Prolonged labor	17	2
Pitocin stimulus	7	1
Previous section	34	24
Elderly 0000	12	2
Lack of progress	16	3
Other	6	1
Total	659	325

Another factor which may be of importance is that in this study the patients with a clinical diagonal conjugate of over 11.5 cm. had a higher average fetal weight. In this group it was 3,272 grams while in the lower group it

was 3,100 grams. The largest baby in the longer C.D. group weighed between 5,500 grams and 5,999 grams, while the largest in the smaller C.D. group weighed under 5,000 grams. Statistically, this is of no significance.

One other phase of this discussion deserves some comment. In 5 of the purely elective sections done in patients with a C.D. over 11.5 cm. there were abnormal presentations, 3 breech and 2 face. In the 30 purely elective sections in the group of patients with a diagonal conjugate of 11.5 cm. and under there were 6 breech presentations and 1 brow. Probably these should be included in the obstructed group and this would still increase the difference in the percentages of obstructed labor.

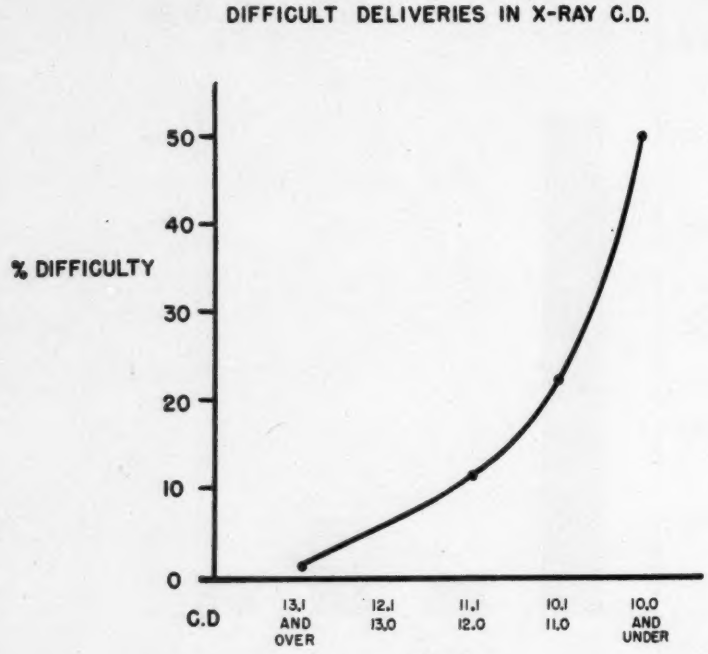


Fig. 9.

X-ray C.D. and Clinical Results

To complete the study of the diagonal conjugate, 690 patients in whom the x-ray C.D. was measured were analyzed similarly. Fig. 9, and Tables VI, VII, and VIII show the percentage of difficulty encountered in the various levels. This graph appears to be much more reasonable in that the lower the x-ray C.D. the higher the percentage of obstructed labors. These results are no more than one would expect.

Discussion

The foregoing results were to us in some respects somewhat of a surprise. The corroboration of Dippel's work on the relationship of the x-ray C.D. to the C.O. was expected. For the most part this material also agrees with Dippel's results as to relationship of the clinical C.D. over 11.5 cm. and the x-ray C.O. However, it is not to be expected that with every patient who has a clinical diagonal conjugate of over 11.5 cm. there will be no pelvic difficulty at the inlet, and one should not be lulled into complacent security by a supposedly satisfactory clinical measurement.

TABLE VI. CLINICAL RESULTS WITH X-RAY C.D.

TYPE OF DELIVERY	10.0 CM. AND LESS	10.1-11.0	11.1 - 12.0	12.1 - 13.0	13.1 AND OVER
Easy	2	27	163	178	182
Difficult	0	3	18	13	7
Sections without labor	5	11	25	16	7
Sections with labor	2	4	23	18	3

TABLE VII. FETAL DEATHS IN X-RAY C.D.

TYPE OF DELIVERY	10.0 CM.	10.1-11.0	11.1-12.0	12.1-13.0	13.1 AND OVER
Easy	0	0	2	0	0
Difficult	0	2	1	2	0
Sections with labor	0	0	0	0	0

TABLE VIII. OBSTRUCTED LABOR IN X-RAY C.D.

TYPE OF DELIVERY	10.0 CM. AND LESS	10.1-11.0	11.1-12.0	12.1-13.0	13.1 AND OVER
This pregnancy	1	4	17	7	1
Previous pregnancies	1	2	1	3	1
Number of difficult cases	2	8	21	12	2
Per cent	50	22	11	6	1

The accuracy of the clinical diagonal conjugate leaves something to be desired. We had felt rather comfortable in the feeling that clinical evaluation of the pelvis was moderately accurate and when such a pelvis was satisfactory, one need not be on the alert for possible disproportion at the inlet. Most of the clinical measurements of the diagonal conjugate that were done by the visiting staff in our dystocia clinic were by men who have especially trained themselves for this particular clinic. In other words, I believe that the clinical evaluations of these pelves in most instances were well done, but as one can see from the above, even the most careful scrutinization of the pelvis clinically may well be a poor one from the standpoint of the x-ray.

Obviously this analysis of the results of the clinical diagonal conjugates will not stand up, because of the selectivity of the group. It does not seem out of place, however, to state that because the clinical diagonal conjugate is above 11.5 cm. does not necessarily mean that no inlet disproportion or contraction, whichever term you prefer, can occur. I do not believe that this means it happens rarely, rather let us say infrequently.

Since x-ray examination of any pelvis is more accurate than clinical evaluation, one would expect a more reasonable clinical result using the x-ray C.D., and this is held true. But one cannot, even by x-ray, predict in 100 per cent of the cases the actual outcome without labor, as witness 50 per cent satisfactory (mother well and baby not damaged) results when the x-ray C.D. was 10.0 cm. or below.

Summary

The diagonal conjugate has been analyzed from the following viewpoints: (1) evaluation of Smellie's rule; (2) the relationship of the clinical C.D. to

the x-ray C.D.; (3) the accuracy of the clinical C.D.; (4) the relationship of the clinical C.D. to the x-ray C.O.; (5) the clinical results of the clinical C.D.; and (6) the clinical results of the x-ray C.D.

Conclusions

1. Smellie's rule is inaccurate and can be fraught with danger in inlet contraction.

2. Clinical evaluation of the diagonal conjugate is grossly inaccurate.

3. Vaginal delivery with the clinical C.D. above 11.5 cm. can be expected in most instances.

4. Vaginal delivery with the clinical C.D. below 11.5 cm. can be expected in 91.4 per cent of all patients.

5. The x-ray is obviously a more accurate method of determining the diagonal conjugate.

6. Only routine x-ray pelvimetry can demonstrate *all* suspect pelves.

7. X-ray pelvimetry is only an adjunct to the clinical prognosis of labor and interpretation of x-ray films should not be used for elective interruption of pregnancy except in abnormal presentations.

References

1. Jacobs, B.: Am. J. Obst. & Gynec. 29: 227, 1934.
2. Jacobs, B.: Am. J. Obst. & Gynec. 32: 76, 1936.
3. Jacobs, B.: Am. J. Obst. & Gynec. 43: 267, 1942.
4. Dippel, A. L.: Surg., Gynec. & Obst. 68: 643, 1939.
5. Eastman, N. J.: Williams Obstetrics, ed. 10, New York, 1950, Appleton-Century Crofts, Inc.

THE CLINICAL EVALUATION OF THE USE OF METHYLERGONOVINE TARTRATE (METHERGINE) WITH CALCIUM GLUCONOGALACTO-GLUCONATE (NEO-CALGLUCON) FOLLOWING THE THIRD STAGE OF LABOR*†

HOWARD V. SANDIN, M.D., AND JOSEPH A. HARDY, M.D.,
ST. LOUIS, MO.

(From the Department of Gynecology and Obstetrics St. Louis University)

HEMORRHAGE, next to infection, is the most common cause of maternal mortality.[19]

It should be the duty of every physician not only to reduce the incidence of postpartum hemorrhage but also to decrease average blood loss,[4] for there is definite correlation between excessive blood loss and puerperal morbidity.[4]

This study was prompted by a desire for a more effective method of reducing blood loss immediately following the third stage of labor.

The appropriate procedure should not only minimize blood loss but should approximate normal physiological processes and thus reduce toxic side effects. It should also be so simple in application that it can be used in small general hospitals.

The critical component of the procedure of this study stems from the results of animal experimentation by Danforth and Ivy,[7] and from clinical studies of Patton and Mussey,[14] and Hart and Noble.[10]

Danforth and Ivy[7] have shown in their investigations that calcium is necessary for the maintenance of tone and contractility of the postpartum uterus in dogs and rabbits. They have demonstrated that if available calcium is reduced the uterus does not contract; that calcium administered intravenously potentiates the oxytocic action of Pitocin, ergonovine, and histamine; and, last, that normal adequate amounts of the customary oxytocics are ineffectual if available calcium is diminished.

Patton and Mussey[14] administered intravenous calcium gluconate in labor and in labor complicated by uterine inertia and concluded that calcium will increase the intensity of uterine contraction and found calcium especially useful in cases of uterine inertia during the first and second stages of labor.

Hart and Noble[10] employed intravenous calcium gluconate to initiate labor, and during labor, and likewise found it useful. These two investigators also used intravenous calcium gluconate in fourteen cases of postpartum hemorrhage occurring immediately to nine hours following delivery. In a

*The methylergonovine tartrate (Methergine) and calcium gluconogalactogluconate (Neo-Calglucon) employed in this study were provided by Sandoz Pharmaceuticals, division of Sandoz Chemical Works, Inc.

†An abridgment of thesis submitted by Howard V. Sandin to the Faculty of the Graduate School of St. Louis University in partial fulfillment of the requirements for the degree of Master in Gynecology and Obstetrics.

number of these cases where customary oxytocics had failed to contract the uterus, the addition of calcium gluconate intravenously produced dramatic cessation of hemorrhage.

According to Reynolds[3] the action of hormones or drugs upon uterine muscle involves one of two responses, namely, augmentation or depression of contractility. In the former, either an initiation or an intensification of one of the normal patterns of uterine movements, or a mass response (simultaneous contraction) of the whole organ may take place. In no case, however, will the effect of a given hormone (or drug) invariably result from its administration unless certain physiological conditions exist within the uterus. These factors are variable and taken together are related to the degree of irritability of the uterine musculature at the time of administration of the hormone or drug.

There has been much theorizing on the role of inorganic chemical constituents of muscle tissue and upon the characteristics of muscle activity. This is especially true of uterine muscle where the high calcium content has led to the view that this ion is the primary stimulant of automatic activity.

The specificity of the action of calcium on uterine muscle cannot be denied. In view of the aforementioned investigations, both clinical and experimental, the investigators adopted a procedure which administers intravenously a calcium salt with an oxytocic to reduce blood loss immediately following the third stage of labor.

In employing this method the investigators endeavored to establish a predominantly physiological rather than a predominantly empirical approach to the problem of reducing blood loss immediately following the third stage of labor.

Our review of the literature reveals no record utilizing the intravenous administration of a calcium salt (calcium gluconogalactogluconate) in combination with an intravenous oxytocic (methylergonovine) in the manner which has been employed in this study.

History, Chemistry, and Properties of Materials Used

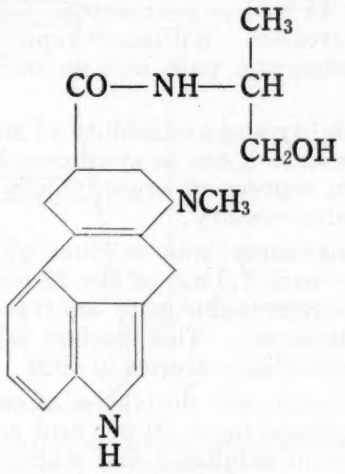
Oxytocics, drugs which stimulate the motility of the uterus,[2] have been used routinely in recent years especially with the advent of obstetrical analgesia as well as anesthesia to control postpartum hemorrhage and reduce blood loss, to aid in the normal involution of the uterus, to reduce postpartum morbidity, and for induction of labor at term when such a step is indicated.

There are many known drugs which are oxytocic. However, there is a group of drugs which have a pronounced selective effect on uterine motility and these comprise the clinical oxytocics.[2] Of these, three alkaloids of ergot, namely, ergotoxine, ergotamine, ergonovine, and the oxytocic principle extracted from the posterior lobe of the hypophysis are most important.[2]

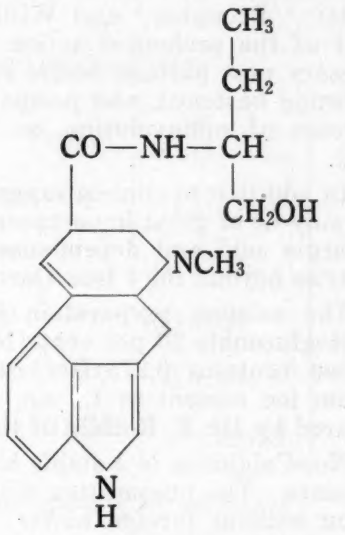
Ergonovine, because of low toxicity and rapid and sustained action, has replaced the posterior pituitary extract as well as all other ergot preparations. Reich[15] in 1939 clearly demonstrated the advantages of ergonovine over other oxytocics. In 1943, however, Stoll and Hofmann[18] synthesized a semisynthetic ergot alkaloid, methylergonovine tartrate (Methergine). Methergine is the

first semisynthetic ergot alkaloid made available for therapeutic use. Clinical investigations have shown Methergine to be superior to ergonovine and for this reason it was chosen as the oxytocic for the control series in this study.

Methergine is the tartrate of methylergonovine, a homologue of ergonovine. Chemically the base is a d-lysergic acid (+) hydroxybutylamide-(2). It differs from ergonovine in that it contains a butanol amide-(2) group instead of a propanol amide-(2) group. The following formulas show differences between the two homologues.



Ergonovine



Methergine

The pharmacological properties of Methergine have been extensively studied by Kirchhof, Racely, Wilson, and David,[12] who found Methergine similar to ergonovine. Both have marked specific uterotonic action. Their mode of action is a direct stimulation of uterine musculature and both have a slight adrenergic action without sympatholytic action. Additional pharmacological studies of Kirchhof, David, Phatak, and Racely[13] have shown Methergine to have low toxicity and to be well tolerated in dosages in excess of those used clinically. Clinical studies of many investigators[5, 6, 9, 12, 20, 21, 22] have shown Methergine to be unattended by toxic side effects or undesirable side reactions.

Although pharmacologically Methergine and ergonovine appear equal in uterotonic effect, clinical investigators have found Methergine to be superior. Gill[9] compared the effects of Methergine with those of ergonovine on postpartum (human) uteri by measuring intensity and duration of uterine contraction by means of an intrauterine bag and a manometer. Gill[9] reported that Methergine caused contractions 1.5 times stronger and 1.3 times longer in duration than those of ergonovine.

Roberts[17] reported contractions of the fundus after Methergine stronger and longer than those after ergonovine. Cartwright and Rogers[6] reported Methergine equaled ergonovine in speed of action but surpassed ergonovine in intensity and duration of contraction. Similarly Kirchhof, Racely, Wilson, and David[12] found clinically that Methergine surpassed ergonovine in duration and intensity of action.

Comparative studies between Methergine and ergonovine have shown Methergine to be more effective in respect to blood loss. Reductions in blood loss have been reported by the clinical investigations of Roberts,[17] Cartwright and Rogers,[6] Williams,[22] Hepp and Evans,[11] and Riordan, Stricker, Correnti, and Torkelson.[16] Tritsch and Schneider[20] and Tritsch, Schneider, and Longworth,[21] Tollefson,[19] and Gipstein[8] report a reduction of blood loss with Methergine as compared to "other available statistics."

Shortened third stages of labor with use of Methergine are reported by Kirchhof, Racely, Wilson, and David,[12] Tritsch and associates,[20, 21] Roberts,[17] Gipstein,[8] Brougher,[5] and Williams.[22] Gipstein[8] further reported that as a result of the prolonged action of Methergine, less oxytocic medication was necessary post partum, lochia was decreased, as well as postpartum bleeding, involution hastened, and postpartum pain decreased. Williams[22] reported no incidence of subinvolution, no increased postpartum pain and no increased lochia.

In addition to clinical superiority, the stability and availability of Methergine may be of great importance in the future since it can be synthesized from d-lysergic acid and dependence upon foreign sources of ergot, chiefly from countries beyond the "Iron Curtain," will be unnecessary.

The calcium preparation chosen for this study was calcium gluconogalactogluconate 20 per cent (Neo-Calglucon—each 1.0 c.c. of the 20 per cent solution contains 0.275 Gm. calcium gluconogalactogluconate equivalent in calcium ion content to 1.0 c.c. of calcium gluconate). This calcium salt was prepared by Dr. E. Rothlin of the Sandoz research laboratories in 1920.

Neo-Calglucon is a stable highly soluble double salt derivative of calcium gluconate. The preparation will remain in solution up to 20 per cent concentration without foreign buffer. These factors of solubility and stability are important from the standpoints of absorption of calcium and of safety in administration.

The structural formulas for calcium gluconogalactogluconate and calcium gluconate are shown in Fig. 1 with a diagrammatic illustration of their differences in solubility.

Method of Investigation

Two series of fifty cases each were observed and designated series M and series M-N depending upon the medication received.

The control series M received 1.0 c.c. (0.2 mg.) of Methergine* injected intravenously rapidly as the placenta crowned following natural separation.

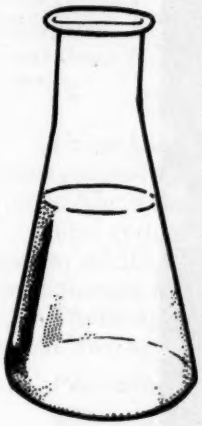
Patients of series M-N received 10 c.c. of 20 per cent Neo-Calglucon† intravenously in the same vein immediately following the injection of 0.2 mg. of Methergine. The Neo-Calglucon was injected slowly over a period of 3 to 5 minutes. In both series the moment of injection of Methergine was timed.

Blood was collected in both series for 15 minutes following delivery of the placenta, in the following manner and carefully measured. A sterile Monel steel pan was placed beneath the patient's buttocks. A tapered, flanged, curved trough extended from the pan and emptied into a graduated container. The graduated container was placed in a ring at the end of a movable metal arm under the direct vision of the accoucheur, and could be rapidly maneuvered by the operator's knee to avoid inclusion of other diluents, e.g., amniotic fluid or bleeding from the episiotomy wound.

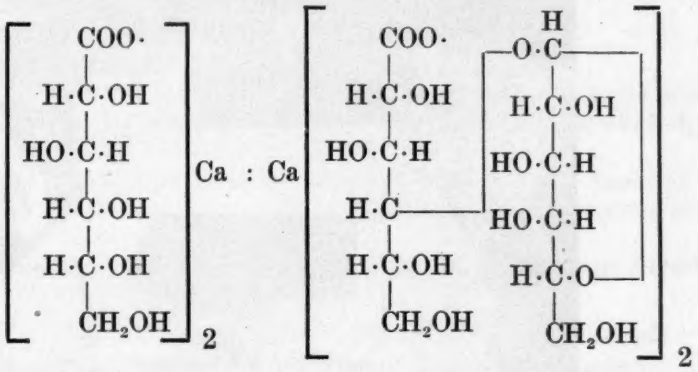
*Methylergonovine.
†Calcium gluconogalactogluconate.

Immediately upon completion of the placental delivery the accoucheur displaced the corpus uteri xiphoidward by placing the fingers of one hand between fundus and symphysis and exerting pressure elevating the uterus. This maneuver was aided momentarily by simultaneously exerting upward pressure through the anterior fornix with two fingers of the opposite hand. The vaginal hand was then quickly withdrawn and immediately placed over the elevated fundus. The fundus was gently massaged until contraction ensued and the time of occurrence of this first contraction was noted.

Every attempt was made to keep the technique constant in each series so that results are comparable.

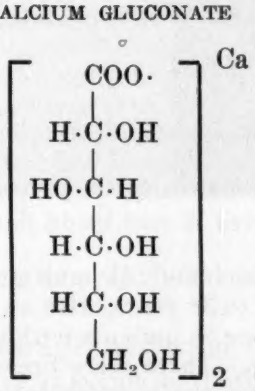


CALCIUM GLUCONO-GALACTOGLUCONATE



30 Gm. of Calcium gluconogalactogluconate dissolve *readily* in 100 c.c. H_2O at ordinary temperatures.

CALCIUM GLUCONATE



10 Gm. of Calcium gluconate do *not* dissolve in 100 c.c. H_2O at ordinary temperatures.

Fig. 1.

Our primary observations were made with respect to (1) blood loss, (2) contraction time of the uterus, (3) character of the uterine contraction, (4) effect on blood pressure, and (5) toxic manifestations.

During the first three days of the puerperium the patients of each series received one Methergine tablet twice daily, each tablet containing 0.25 mg. methylergonovine tartrate.

Subsequent observations were made during the puerperium with respect to (1) requirements for relief of afterpains, (2) the amount and character of lochia, and (3) uterine involution. Fig. 2 is an illustration of the apparatus used to collect blood.

Clinical Results

Résumé of Clinical Material.—

This study includes 100 unselected cases of vaginal deliveries of full-term or premature infants, from the clinical service at Firmin Desloge Hospital, St. Louis University.

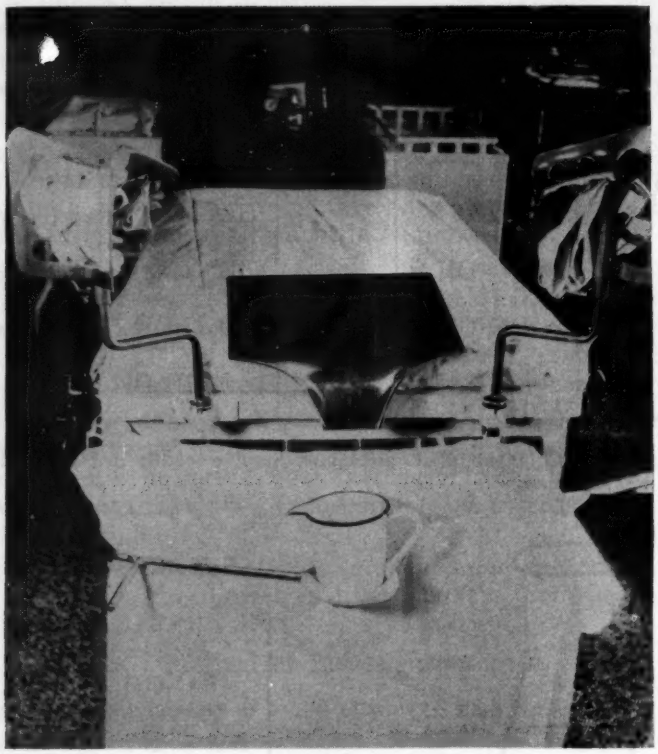


Fig. 2.

Series M included 31 multigravidas and 19 primigravidas whose ages ranged from 16 to 38 years, with an average age of 24.68 years. Two deliveries in this series were in patients with pre-eclampsia. In four deliveries the labors were premature. Three were breech presentations with the remaining forty-seven deliveries cephalic presentations.

Series M-N included 39 multigravidas and 11 primigravidas whose ages ranged from 17 to 38 years, with an average of 25 years. In seven deliveries in this series there were premature labors. There was one case of postmature labor with eclampsia and one case of low-lying placenta with slight bleeding during *early* labor. There were four breech presentations and the remaining forty-six deliveries were cephalic presentations.

Comparison of Average Blood Loss Between M Series and M-N Series.—

Table I records the average blood loss in M and M-N series for the total cases in each series and according to parity, as well as the percentage of reduction of blood loss in M-N series over blood loss in M series.

As indicated by this table, the average blood loss in M series was 83.42 c.c., 84.67 c.c. and 84.2 c.c. for primigravidas, multiparas, and total cases, respectively, while in series M-N, the average blood loss was 36.36 c.c., 34.87 c.c., and 35.61 c.c., respectively, for the same categories.

TABLE I. AVERAGE BLOOD LOSS, M SERIES AND M-N SERIES, WITH PERCENTAGE OF REDUCTION OF BLOOD LOSS IN M-N SERIES

	M SERIES		M-N SERIES		PERCENTAGE OF REDUCTION OF BLOOD LOSS IN M-N SERIES
	NO. CASES	AVERAGE BLOOD LOSS	NO. CASES	AVERAGE BLOOD LOSS	
Primigravidas	19	83.42 c.c.	11	36.36 c.c.	43.57
Multiparas	31	84.67 c.c.	39	34.87 c.c.	41.10
Total Cases each series	50	84.20 c.c.	50	35.61 c.c.	42.29

From analysis of Table I, it is evident that the addition of Neo-Calglucon* intravenously following Methergine† in the M-N series has significantly reduced blood loss as compared to that of M series.

The reduction of blood loss is 42.29 per cent for the total cases of each series, 41.10 per cent for the primigravidous cases, and 43.57 per cent for the multiparous cases.

There appears to be little significant difference in the average blood loss in the two series when analyzed according to parity.

Percentage of Cases Grouped at 25.0 c.c. Actual Blood Loss Levels.—

The blood loss as calculated on a percentage basis of the number of patients grouped at 25.0 c.c. actual blood loss levels is presented in Table II. The blood loss difference between the two series of cases becomes more significant when the cases are broken down into these smaller blood loss levels.

This fact is strikingly illustrated in the total cases of each series, by the following examples: forty-eight per cent of the patients of the M-N series had blood loss of 0 to 25.0 c.c. whereas less than one-half of this number, or only 22 per cent of the M series patients lost less than 0 to 25.0 c.c. Similarly, 78 per cent of the patients of M-N series had blood loss 0 to 50.0 c.c., whereas only 48 per cent of the patients of M series fall into that category. One hundred per cent of the patients of M-N series had blood loss of less than 125.0 c.c. whereas only 80 per cent of the patients of M series fall into that group.

Only two patients in the M-N series had blood loss of over 100.0 c.c., one with 115.0 c.c. and one with 120.0 c.c.

Two patients of M series had blood loss of over 250.0 c.c.; one 350.0 c.c.; and one 400.0 c.c.

Contraction Time of the Uterus and Character of Uterine Contraction.—

The period of time elapsing between the injection of Methergine and contraction of the uterus was designated the contraction time.

Table III summarizes the average contraction for the total cases of each series and according to parity in each series.

It is significant to note that the uteri of the M-N series responded appreciably faster than did those of the M series, as illustrated by the difference in the average contraction time of the total cases of the M-N and M series. This observation demonstrates the synergistic oxytocic action of calcium. A negligible difference in average contraction time between primigravidas and multiparas is noted in both series.

*Calcium gluconogalactogluconate.
†Methylergonovine.

TABLE II. PERCENTAGE OF CASES GROUPED AT 25.0 C.C. ACTUAL BLOOD LOSS LEVELS

NO. C.C. LOSS BLOOD	PRIMIGRAVIDAS				MULTIPARAS				TOTAL CASES			
	M SERIES		M-N SERIES		M SERIES		M-N SERIES		M SERIES		M-N SERIES	
	NO. PTS.	PER CENT OF TOTAL CASES	NO. OF CASES	PER CENT OF TOTAL CASES	NO. PTS.	PER CENT OF TOTAL CASES	NO. OF CASES	PER CENT OF TOTAL CASES	NO. PTS.	PER CENT OF TOTAL CASES	NO. OF CASES	PER CENT OF TOTAL CASES
0- 25	3	15.7	6	54.5	8	25.8	18	46.1	11	22.0	24	48.0
26- 50	4	21.0	2	18.1	9	29.0	13	33.3	13	26.0	15	30.0
51- 75	6	31.5	2	18.1	2	6.4	5	12.8	8	16.0	7	14.0
76-100	3	15.7	0	0	4	12.9	2	5.1	7	14.0	2	4.0
101-125	0	0	1	9.0	1	3.2	1	2.5	1	2.0	2	4.0
126-150	1	5.2	0	0	1	3.2	0	0	2	4.0	0	0
151-175	0	0	0	0	1	3.2	0	0	1	2.0	0	0
176-200	0	0	0	0	3	9.6	0	0	3	6.0	0	0
201-225	0	0	0	0	1	3.2	0	0	1	2.0	0	0
226-250	1	5.2	0	0	0	0	0	0	1	2.0	0	0
Over 251	1	5.2	0	0	1	3.2	0	0	2	4.0	0	0

It was further observed that in the M-N series the uteri contracted more firmly (with extreme hardness) than did the uteri of the M series. This observation can be correlated with the difference in the average blood loss and contraction time between M-N series and M series. The fundi in both series remained firmly contracted throughout a minimum of the first postpartum hour. There were no cases of uterine atony or postpartum hemorrhage in either series.

TABLE III. AVERAGE UTERINE CONTRACTION TIME IN M-N SERIES AND M SERIES

	M SERIES		M-N SERIES		TOTAL CASES	
	PRIMIGRAVIDAS	MULTIPARAS	PRIMIGRAVIDAS	MULTIPARAS	M SERIES	M-N SERIES
Contraction time in seconds	73.15	74.83	59.09	62.69	73.00	61.90

Comparison of Blood Pressure Between M Series and M-N Series.—

The patients' blood pressures were taken in both series of cases immediately or very shortly after delivery. These blood pressure readings were compared with the patients' blood pressures taken on admission to the obstetrical division.

Blood pressures were interpreted to be the *same* if there was no greater difference than 10 mm. of mercury of the systolic or diastolic pressure reading. If the change in systolic or diastolic pressure reading was greater than 10 mm. of mercury, the pressure was interpreted as being elevated or lowered as the case may be.

Table IV reveals no significant difference between M series and M-N series with respect to the effect of the administration of calcium on blood pressure.

It is also interesting to note that the majority of cases in both M series and M-N series showed no significant pressor effect as usually seen when other oxytocics or combinations of oxytocics are employed.

Requirements for Relief of Afterpains in M Series and M-N Series.—

Codeine, ½ grain, and acetylsalicylic acid, 10 grains, were given on demand to all patients requiring relief of afterpains in both M and M-N series.

The number of patients requiring medication for afterpain as calculated on a percentage basis is presented in Table V. Table V reveals the percentage of patients in M and M-N series requiring relief with respect to the total number of cases in each series and according to parity in each series for the day of delivery, and for the first three days of the puerperium during which time each patient received one Methergine tablet (0.25 mg. methylergonovine) twice daily.

In neither series did any patients require more than two doses of medication daily.

The primigravidas of both M and M-N series required only a single dose through the second day with no medication on the third day. In both M and M-N series a higher percentage of multiparous patients required medication than did the primigravidas. It is evident throughout both series that requirements for relief of afterpain were minimal and closely paralleled each other; a slightly higher percentage of the total patients of the M-N series required medication for afterpains than did those total patients of the M series.

Observations Upon Uterine Involution and Lochia in M Series and M-N Series.—

The height of the fundus above the symphysis pubis was measured every other day in the majority of cases of both M and M-N series.

TABLE IV. COMPARISON OF BLOOD PRESSURES BETWEEN M SERIES AND M-N SERIES ON PERCENTAGE BASIS

BLOOD PRESSURE	M SERIES				M-N SERIES				TOTAL CASES			
	PRIMIGRAVIDAS		MULTIPARAS		PRIMIGRAVIDAS		MULTIPARAS		M SERIES		M-N SERIES	
	NO. OF CASES	PER CENT OF TOTAL	NO. OF CASES	PER CENT OF TOTAL	NO. OF CASES	PER CENT OF TOTAL	NO. OF CASES	PER CENT OF TOTAL	NO. OF CASES	PER CENT OF TOTAL	NO. OF CASES	PER CENT OF TOTAL
Same	12	63.15	17	54.83	5	50.0	26	66.66	29	58.0	31	63.2
Elevated	3	15.78	7	22.58	1	10.0	11	28.20	10	20.0	12	24.4
Lowered	4	21.05	7	22.58	4	40.0	2	5.12	11	22.0	6	12.2

TABLE V. PERCENTAGE OF CASES REQUIRING MEDICATION FOR "AFTERPAINS" M SERIES AND M-N SERIES

	DOSES OF MEDICATION	PRIMIGRAVIDAS				MULTIPARAS				TOTAL CASES			
		M SERIES		M-N SERIES		M SERIES		M-N SERIES		M SERIES		M-N SERIES	
		NO. OF PTS.	PER CENT OF TOTAL	NO. OF PTS.	PER CENT OF TOTAL	NO. OF PTS.	PER CENT OF TOTAL	NO. OF PTS.	PER CENT OF TOTAL	NO. OF PTS.	PER CENT OF TOTAL	NO. OF PTS.	PER CENT OF TOTAL
Day of delivery	1	2	10.52	1	9.09	4	12.9	6	15.3	6	12.0	7	14.0
	2	0	0	0	0	0	0	0	0	0	0	0	0
First postpartum day	1	1	5.26	2	18.18	12	38.7	15	38.4	13	26.0	17	34.0
	2	0	0	0	0	6	19.3	9	23.0	6	12.0	9	18.0
Second postpartum day	1	1	5.26	1	9.09	12	38.7	16	41.0	13	26.0	17	34.0
	2	0	0	0	0	5	16.2	1	2.5	5	10.0	1	2.0
Third postpartum day	1	0	0	0	0	8	25.8	4	10.2	8	14.0	4	8.0
	2	0	0	0	0	1	3.2	0	0	1	2.0	0	0

In general there was an average reduction of 1 to 2 cm. in the height of the fundus on each successive measurement, and by the seventh postpartum day the height of the fundus averaged 10.0 cm. in the M series and 10.5 cm. in the M-N series.

There appeared to be slightly less reduction in the fundal height with the M-N series and this may be attributed to the fact that a greater percentage of cases in this series were multiparas, and that the uteri contracted more firmly from the beginning as the result of the specific action of "calcium" upon the uterus.

The uterus was pelvic in one case of the M series by the seventh postpartum day. Two such cases were noted in the M-N series.

Forty-two per cent of the patients of M series returned for postpartum examination between 4 to 11 weeks. In every case the uterus was completely involuted. Thirty-eight per cent of the patients of the M-N series returned for postpartum examination between 4 and 12 weeks. In every case the uterus was completely involuted.

It was our observation, and the opinion of the nursing supervisor and nursing staff that lochia in both M series and M-N series was less than that noted in private patients receiving other oxytocics post partum.

It was observed that patients in both M series and M-N series required fewer changes of perineal pads as a result of the lessened lochial flow.

The great majority of the patients of both M series and M-N series left the hospital on the seventh postpartum day with a scant serosanguineous vaginal discharge or lochia serosa.

Systemic Toxic Manifestations.—

No undesirable systemic reactions were observed in the M series or M-N series.

In the M-N series three patients (6 per cent) experienced nausea and two (4 per cent) experienced nausea and vomited their gastric contents during the injection of Neo-Calglucon. Nausea was a transient experience in the cases in which it was not followed by emesis.

A small number of patients in the M-N series experienced a sensation of warmth of the skin and a few noted a metallic taste in the mouth during the injection of the Neo-Calglucon if the injection was rapid.

These systemic manifestations were readily controlled by slow injection of the calcium salt and were not considered a contraindication for further administration of calcium.

Summary and Discussion

A method of reducing blood loss by administering intravenously a calcium salt (Neo-Calglucon) with an oxytocic (Methergine) immediately following the third stage of labor is presented.

The intravenous administration of the calcium salt (Neo-Calglucon 20 per cent) immediately following the intravenous administration of the oxytocic (Methergine) to the fifty patients of the M-N series reduced average blood loss 42.29 per cent as compared to the average blood loss of the fifty patients of the M series, which was the control series.

The difference in blood loss between M series and M-N series becomes more apparent when compared on a percentage basis at low actual blood loss levels. For example, this difference is illustrated by the observation that 48 per cent of the patients of the M-N series had blood loss of 25.0 c.c. or less, whereas only 22 per cent of the M series had 25.0 c.c. or less blood loss.

No appreciable difference in the average blood loss in the two series is noted when analyzed according to parity.

The addition of the intravenous calcium salt appreciably shortened the average uterine contraction time in the M-N series as compared to the average contraction time of the control series.

No significant difference in the average uterine contraction time was noted in the two series when analyzed according to parity.

The uteri of the M-N series contracted more firmly than did the uteri of the control series. This observation can be correlated with the more rapid uterine contraction time and reduction of blood loss noted in the M-N series as compared to the control series.

There were no cases of uterine atony or postpartum hemorrhage in either series of cases.

There was no significant difference between the two series with respect to the effect of the administration of calcium on blood pressure. It was interesting to note also that the majority of cases in both series showed no appreciable pressor effect as usually seen with other oxytocics or combination of oxytocics.

In general the requirements for the relief of afterpain were minimal in both M and M-N series.

In no instance did a patient in either series require more than two doses of medication daily during the three-day course of Methergine tablets post partum. Only one patient in the M series required a second dose of medication on the third puerperal day.

No primigravida required more than a single dose of medication daily in either series, and none required medication beyond the second puerperal day.

A higher percentage of multiparas required medication than did the primigravidas in both series of cases; but the difference in percentage between multiparas of each series is not significant.

In the total cases of each series a slightly higher percentage of the M-N series required medication than of the M series. Although the difference on a percentage basis between the two series is not marked, it is indicative of a slight increase in irritability or sensitivity of the uteri in the patients receiving calcium. In view of the over-all minimal requirements for the relief of afterpain, this observation is not considered a disadvantage of the method or an undesirable side effect.

Uterine involution progressed satisfactorily in both M series and M-N series. The height of the fundi (above the symphysis) averaged 10.0 cm. and 10.5 cm. for the M series and the M-N series, respectively, by the seventh postpartum day.

It is observed by the authors, nursing supervisor, and nursing staff that patients of both series had less lochia and required fewer changes of perineal pads than did the private patients who received other oxytocics post partum.

The majority of patients of both series left the hospital with only a scant serosanguineous vaginal discharge or with lochia serosa.

Forty-two per cent of the patients of M-series returned for postpartum examination between 4 and 11 weeks, and in every case the uterus was completely involuted.

Thirty-eight per cent of the patients of M-N series returned for postpartum examination between 4 and 12 weeks, and in every case the uterus was completely involuted.

No significant systemic manifestations or untoward side reactions were observed in M series or in M-N series.

Three patients experienced a transient nausea and two experienced nausea and emesis during the injection of Neo-Calglucon in the M-N series. A small number of patients of M-N series experienced a sensation of warmth of the skin and/or a slight metallic taste in the mouth if the Neo-Calglucon injection was rapid. These systemic manifestations were readily controlled by slower injection of the calcium salt and were not a contraindication to continuance of injection.

The only suggested contraindication to the intravenous administration of calcium is in the case of individuals receiving digitalis therapy. Calcium, like digitalis, increases systolic contraction of the heart and fear of a dangerous potentiating effect (systolic arrest) is the basis for the contraindication in digitalized patients.[1]

References

1. Friedberg, C. K.: Diseases of the Heart, Philadelphia, W. B. Saunders Company.
2. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, ed. 2, 1943, The Macmillan Company.
3. Reynolds, S. R. M.: Physiology of the Uterus, ed. 2, New York, 1949, Paul B. Hoeber, Inc.
4. Stander, H. J.: Textbook of Obstetrics, 3rd revision, New York, 1945, D. Appleton-Century Company.
5. Brougher, J. C.: West. J. Surg. 55: 371, 1947.
6. Cartwright, E. W., and Rogers, W. C.: West. J. Surg. 54: 59, 1946.
7. Danforth, D. N., and Ivy, A. C.: Am. J. Obst. & Gynec. 37: 194, 1939.
8. Gipstein, B. L.: Am. J. Obst. & Gynec. 54: 1065, 1947.
9. Gill, R. C.: J. Obst. & Gynaec. Brit. Emp. 54: 482, 1947.
10. Hart, B. F., and Noble, V.: Am. J. Obst. & Gynec. 45: 692, 1943.
11. Hepp, L. C., and Evans, J. R.: Rocky Mountain M. J. 42: 949, 1945.
12. Kirchhof, A. C., Racely, C. A., Wilson, W. M., and David, N. A.: West. J. Surg. 52: 197, 1944.
13. Kirchhof, A. C., David, N. A., Phatak, N. M., and Racely, C. A.: J. Am. Pharm. A. 36: 145, 1947.
14. Patton, G. D., and Mussey, R. D.: Am. J. Obst. & Gynec. 41: 948, 1941.
15. Reich, A. M.: Am. J. Obst. & Gynec. 37: 224, 1939.
16. Riordan, L. M., Stricker, H. C., Correnti, N. A., and Torkelson, H. P.: J. Missouri M. A. 47: 108, 1950.
17. Roberts, P. C.: West. J. Surg. 52: 380, 1944.
18. Stoll, A., and Hofmann, A.: Helvet. chim. acta 26: 944, 1943.
19. Tollefson, D. G.: West. J. Surg. 52: 383, 1944.
20. Tritsch, J. E., and Schneider, E.: Am. J. Obst. & Gynec. 50: 434, 1945.
21. Tritsch, J. E., Schneider, E., and Longworth, E. F.: New York State J. Med. 48: 293, 1948.
22. Williams, B. C.: Rocky Mountain M. J. 44: 207, 1947.

ETIOLOGY OF PRE-ECLAMPSIA-ECLAMPSIA*

III. The Effect of Oral Ingestion of Sodium Chloride and Sodium Bicarbonate by Patients With Toxemia of Pregnancy

WM. J. DIECKMANN, S.B., M.D., R. C. SMITTER, A.B., M.D.,
E. N. HORNER, S.B., M.D., R. E. POTTINGER, B.A., S.M.,
L. RYNKIEWICZ, S.B., S.M., AND R. LUNDQUIST, S.B., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of the University of Chicago, and The Chicago Lying-in Hospital)

THE cause of pre-eclampsia-eclampsia has been attributed by many investigators to the inability of some pregnant patients normally to excrete sodium chloride or the sodium ion. The excessive parenteral injection of sodium chloride in the nonpregnant and pregnant patient will result in edema, hypertension, proteinuria, convulsions, coma, and even death, thus resembling pre-eclampsia-eclampsia. In our first paper we reported that the normal pregnant women had a decreased ability to excrete water which was even more marked in pre-eclamptic patients. In the second paper we stated that in some patients who apparently have pre-eclampsia, intravenous injections of 1,000 ml. of 2.5 per cent sodium chloride solutions for three or more days caused marked increases in weight, edema, blood pressure, proteinuria, and the onset of the various symptoms and signs which are associated with eclampsia. In the susceptible patient the proteinuria increased rapidly and markedly as a result of the sodium chloride injections. However, in some patients who were admitted with the diagnosis of pre-eclampsia, similar injections caused no such changes.

Material

Identical capsules or tablets, containing either 1 Gm. of sodium chloride (2.8 Gm. sodium), 1.0 Gm. of sodium bicarbonate (1.9 Gm. sodium), 1 Gm. of ammonium chloride, or 1 Gm. of a placebo (lactose) were obtained. Patients who showed too rapid weight gain, edema, proteinuria, or hypertension, or a combination of these signs, were given 50 capsules with directions to take seven per day. The containers were numbered from 1 to 4 and only one individual knew the key. The plan was for each patient to have the four different types of tablets. The patients usually started on sodium chloride and the number who received the placebo is much smaller because it was the last capsule given and many of the patients went into labor. The patients were given written and oral instructions as to the method for collecting and measuring a 24-hour specimen of urine at home. They were to bring a small sample of the mixed urine to the doctor for a quantitative determination of protein by a sensitive sulfosalicyclic acid method. The patients in some instances brought in the first morning specimen which was checked for its protein content by the same method. Chlorides, sodium, and potassium were also determined in some of the urine

*Supported in part by the Chicago Lying-in 50th Anniversary Fund for Eclampsia.

specimens. No change was made in the diet or usual routine instructions for normal pregnancy. The patients were told that the medicine would help them. Seventy-six patients took 7 Gm. of sodium chloride a day for one to three weeks; 28 took 7 Gm. of sodium bicarbonate per day for one or more weeks; 59 used 7 Gm. of ammonium chloride per day and 23 took 7 lactose tablets per day for 1 or more weeks.

The mean gain in weight per week was 490 grams (S.D.* 203 grams) and the maximum gain per week was 1,420 grams (S.D. 980 grams) for the patients before any medication was given. The mean gain per week was 1,560 grams (S.D. 1,300 grams) while taking sodium chloride and 820 grams (S.D. 1,560 grams) with sodium bicarbonate. Sodium chloride did cause a slightly greater average increase per week than even the maximum weight gain before any tablets were started. It is surprising, however, that some patients actually lost weight. It must be remembered that all of these patients were pregnant and in the last trimester of pregnancy, which period is characterized by increasing weight in almost all patients. The increases in those patients who took sodium bicarbonate tablets is less than the maximum weight gain, but greater than the average weight gain. The mean gain with the placebo (lactose) was 500 grams (S.D. 950 grams). Some patients continued to gain weight presumably while taking 7 Gm. ammonium chloride daily but the mean weight loss per week was 1,470 grams (S.D. 2,330 grams). These data are given in Fig. 1. The standard deviation for each mean is quite large and the lines for each patient reveal a marked difference in the response of individual patients.

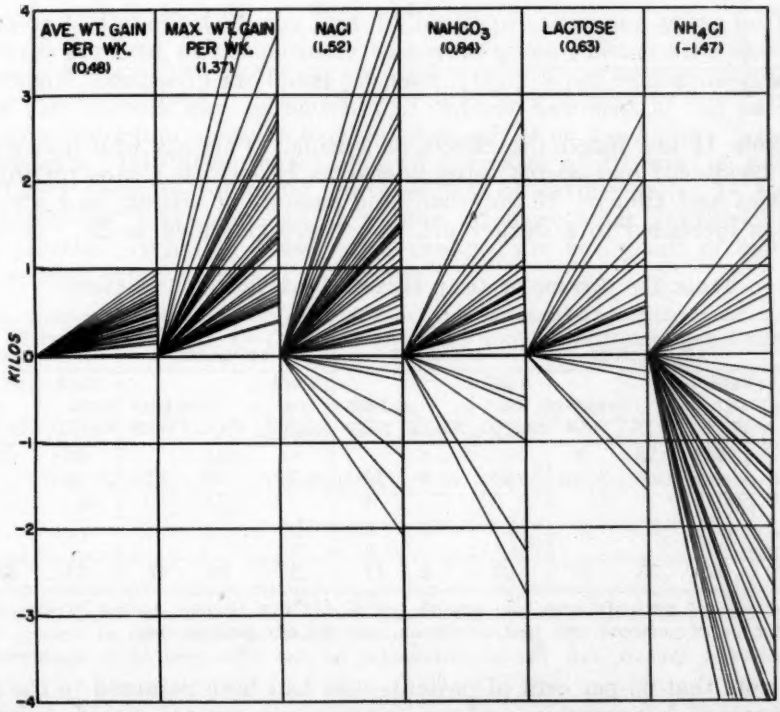


Fig. 1.—Shows the average and maximum changes in weight per week for pregnant patients with presumable toxemia before medication and average changes in weight with each drug.

In Table I are listed the data about patients who showed an increase, decrease, or no change in weight for the week of the study period for the various drugs used. Since these were all pregnant patients in the last trimester of

*Standard deviation.

pregnancy who, as a rule, are gaining weight, it is unusual that some showed no change or even a loss of weight. Seventy-two per cent of the patients who took 7 Gm. of sodium chloride or 7 Gm. of sodium bicarbonate daily showed increases in weight of 500 grams or more and 19 per cent had a loss. A change in weight of 1.5 kilograms (3.3 pounds) or more per week is abnormal; 34 per cent showed gains of this magnitude or more as compared with only 2 per cent showing a loss. There were increases of 500 grams or more in weight in 39 per cent of those who took ammonium chloride, and 55 per cent lost weight. The placebo (lactose) resulted in 61 per cent gaining 500 grams or more and 26 per cent losing weight. Fifteen per cent of the patients taking ammonium chloride and 25 per cent of those taking the placebo gained 1.5 kilograms or more per week.

TABLE I. EFFECT OF ORAL INGESTION ON WEIGHT, PER CENT

CHANGE PER WEEK (KILOGRAMS)	NO CHANGE			INCREASE			DECREASE		
	NaCl OR $NaHCO_3$	NH_4Cl	LACTOSE	NaCl OR $NaHCO_3$	NH_4Cl	LACTOSE	NaCl OR $NaHCO_3$	NH_4Cl	LACTOSE
	2								
0.1-0.49				7	6	13	8	15	18
0.5-0.99				23	12	13	5	2	4
1.0-1.49				15	12	13	4	4	
1.5-1.99				12	2	13	1	6	
2.0-2.99				14	13	22		9	4
3.0-3.99				6			1	15	
4.0-				2				4	
Total per cent	2			79	45	74	19	55	26

In Table II are listed the effects on edema. Patients who had no edema and after treatment had edema were classed as 1+ (which means pitting edema of the ankles and tibia). If they had this amount of edema, and after treatment it was increased to a deeper pit, they were classified as 2+. It was sur-

TABLE II. EFFECT OF ORAL INGESTION ON EDEMA, PER CENT

CHANGE IN DEGREE	NO CHANGE			INCREASE			DECREASE			NONE		
	NaCl OR $NaHCO_3$	NH_4Cl	LAC-TOSE	NaCl OR $NaHCO_3$	NH_4Cl	LAC-TOSE	NaCl OR $NaHCO_3$	NH_4Cl	LAC-TOSE	NaCl OR $NaHCO_3$	NH_4Cl	LAC-TOSE
	32*	33	9							31†	33	57
+				23	4	13	11	19	17			
++				1		4	1	11				
Abdom. wall				1								
Total:	32	33	9	25	4	17	12	30	17	31	33	57

*Percentage of patients who had edema but it did not change during experiments.
†Percentage of patients who had no edema and did not develop any.

prising to note that 63 per cent of patients who had been referred to the toxemia clinic because of hypertension, edema, proteinuria, or too rapid weight gain (600+ grams per week) showed no edema or no change in the degree of edema after the administration of NaCl or $NaHCO_3$; that 66 per cent showed no edema or no change in the degree of edema after ammonium chloride and 66 per cent showed no edema or no change in degree of edema after lactose. We were still more surprised when 12 per cent of patients who had had edema

showed a decrease after the administration of sodium salts. The decrease in edema after ammonium chloride is the usually accepted response but it occurred in only 30 per cent of the cases. It is noteworthy that of 104 patients who received sodium salts 31 per cent had no edema, 32 per cent had no change in the degree, 25 per cent had an increase of edema and 12 per cent a decrease. These were all presumably abnormal patients who had been referred to the toxemia clinic and yet in only 25 per cent was there a presumable association with sodium salts.

TABLE III. EFFECT OF ORAL INGESTION ON THE SYSTOLIC BLOOD PRESSURE, PER CENT

CHANGE MM. HG.	NO CHANGE			INCREASE			DECREASE		
	NaCl OR $NaHCO_3$	NH_4Cl	LACTOSE	NaCl OR $NaHCO_3$	NH_4Cl	LACTOSE	NaCl OR $NaHCO_3$	NH_4Cl	LACTOSE
	12*	11	4						
Normal				21	20	40	21	24	17
1-9				8	5	4	4	9	17
10-19				16	5	4	8	15	14
20-29				8	9		2	1	
30-39					2				
40-49				1					
Total	12	11	4	54	41	48	35	49	48

*Blood pressure was either normal or abnormal but showed no change during experiments.

Data as to the effect on the systolic blood pressure are given in Table III. Thirty-three per cent of the patients who were given sodium salts showed varying degrees of increase in the blood pressure. Only 9 per cent showed significant increases (20 or more mm. of mercury). Sixteen per cent of the patients who were given ammonium chloride had increases of 10 or more mm. Ten per cent of the patients (140/90 or more) showed decreases of 10 mm. or more in the systolic blood pressure following the ingestion of sodium salts; 16 and 14 per cent, respectively, had decreases of 10 mm. or more after ammonium chloride and the placebo. Whether these latter changes are the result of chance or of a psychic effect from a drug is not known.

TABLE IV. EFFECT OF ORAL INGESTION ON THE PROTEINURIA, PER CENT

CHANGE IN DEGREE	NO CHANGE			INCREASE			DECREASE			NONE		
	NaCl OR $NaHCO_3$	NH_4Cl	LACTOSE	NaCl OR $NaHCO_3$	NH_4Cl	LACTOSE	NaCl OR $NaHCO_3$	NH_4Cl	LACTOSE	NaCl OR $NaHCO_3$	NH_4Cl	LACTOSE
	5*									82†	74	90
+				5	13	5	5	6	5			
++				2	6		1					
+++				1								
Total:	5			8	19	5	6	6	5	82	74	90

*No change in amount of proteinuria.
†Percentage of patients who had no proteinuria at any time during experiments.

Data about the occurrence of proteinuria are given in Table IV. It is surprising that over 75 per cent of the patients who had some evidence of toxemia of pregnancy had no proteinuria and did not develop any despite an addition of 7 Gm. of sodium chloride or 7 Gm. of sodium bicarbonate to the usual daily intake of sodium. Furthermore, 17 per cent showed decreases, while 8 per cent showed increases in the amount of protein in the urine but not

to the degree that occurred after intravenous injections of 20-25 Gm. of sodium chloride daily for three or more days. Since these urine specimens were collected at home, we do not believe that a significant difference exists in the percentage of patients who showed an increase or decrease with sodium salts as compared with the placebo. The susceptible or true pre-eclamptic patient in general showed an increase in the proteinuria. This was much more characteristic after the intravenous injection but the amount was usually 20-25 Gm. of sodium chloride daily for three or more days. In true pre-eclamptic patients, proteinuria increased rapidly to as much as 28 Gm. (Chevky-Stafford method) per day (19 Gm. by Kjeldahl) and persisted for days after delivery, which is unusual in pre-eclamptic patients. Ten patients were seen in subsequent pregnancies who had had these tremendous amounts of protein in the urine and the urea clearance and Addis count were normal. Nineteen per cent of the patients showed an increase in proteinuria after the ingestion of ammonium chloride. We have no explanation for this.

Comment

We reported previously that the intravenous injections of sodium lactate or sodium chloride in 20 to 25 Gm. amounts daily for three or more days would cause an increase in weight, edema, blood pressure. and proteinuria in the true pre-eclamptic patient and if the injections were continued would result in the development of the usual symptoms and signs of severe pre-eclampsia. Other patients who had been admitted to the hospital with the diagnosis of pre-eclampsia had similar amounts of the sodium ion injected intravenously but showed no such changes. The present study with the oral ingestion of the sodium ion in addition to the sodium contained in the regular diet has shown that in susceptible patients, who probably have true preeclampsia, increases in weight, edema, blood pressure, and proteinuria occur. The increase in the amount of protein in the urine did not approach that resulting from the intravenous injections of sodium chloride.

It has been taught for many years that the sodium ion is extracellular and if the patient has a marked positive balance for any length of time, edema will appear. The leg and thighs comprise 37 per cent of the body weight and the statement has been made that the increase in body weight must be more than 10 per cent before edema is detectable clinically. Drury and Jones state that fluid accumulation in the legs must increase by 8 per cent before edema becomes evident. Various studies indicate that sodium is not limited to the blood stream and extracellular fluid spaces, but that, if present in excess amounts, it will displace potassium from the cell. Thus, the patient can be storing excessive amounts of sodium without any evidence of pitting edema. So far as we know, no one has been able to demonstrate a direct toxic effect from intracellular sodium because when this occurs other conditions are also altered in the body. Experiments by several investigators have revealed that intracellular changes in water and potassium in the brain cells of the experimental animal will result in convulsions, coma, hyperpyrexia, etc. It must also be kept in mind that this replacement of intracellular potassium by sodium takes place over a period of days or weeks and the final abnormal result may come very abruptly.

One hundred four patients with evidence of toxemia were given sodium chloride or sodium bicarbonate tablets for one or more weeks. Twenty-five per cent of the patients had a final diagnosis of pre-eclampsia, 14 per cent of the patients had a diagnosis of hypertensive disease, and 6 per cent of chronic glomerulonephritis. Fifty-five per cent were considered, despite the signs of toxemia, not to have pre-eclampsia or any other type of toxemia of pregnancy. We cannot state with certainty that every patient took the tablets given to her. However, our results with the intravenous administration of sodium chloride solutions to patients with toxemia, together with the results from the oral ingestion of sodium salts indicate that over 50 per cent of patients with edema, too rapid weight gain, slight hypertension or proteinuria, do not become worse if given increased amounts of sodium chloride and, therefore, do not have pre-eclampsia. At the present time we are not certain what term should be used to designate these patients but suggest "pseudo pre-eclampsia."

Other investigators have suggested that some patients who manifest evidence of toxemia of pregnancy cannot be properly classified as having pre-eclampsia, hypertensive or chronic renal disease. Stander classified these patients as having low reserve kidney which grouping we were all pleased to have him finally discard. However, every investigator who has followed a sufficient number of patients through several pregnancies, one of which at least was complicated by toxemia, has been confronted with the difficulty in classifying patients with slight evidence of toxemia, i.e., for whom we are suggesting the term "pseudo pre-eclampsia." Other investigators are probably placing them in an unclassified group.

Dexter and Weiss cited a case of convulsions in a pregnant woman with essentially normal blood pressure and urine in the presence of marked fluid retention. We would classify this patient from their data as having had eclampsia. We believe that patients with pre-eclampsia and/or eclampsia show some of the following: (1) too rapid and/or excessive weight gain; (2) edema after bed rest; (3) a marked negative water balance after delivery together with a marked decrease in weight. Hypertension and/or proteinuria are not essential to establish this diagnosis. Any one of these will establish the fact that there had been an abnormal retention of water and electrolyte which we believe are concerned in causing pre-eclampsia-eclampsia. Increased blood pressure (hypertension) and/or proteinuria may be present but are not primary.

Excluding a considerable number of patients from the pre-eclamptic group will simplify treatment. It will improve maternal and fetal mortality, i.e., by decreasing the number of inductions of labor or cesarean sections for questionable toxemia. It will also make the results of follow-up studies more logical, thereby causing unification of thought.

Summary

Pregnant patients who showed too rapid weight gain, edema, hypertension, proteinuria, or various combinations of these signs were given sufficient identical 1 Gm. tablets* of sodium chloride, sodium bicarbonate, ammonium chloride, or

*Some of the tablets were donated by Eli Lilly & Company, Indianapolis, Ind.

a placebo. Instructions were that they were to take 7 tablets per day for one or more weeks and each patient was, if possible, to have taken the series of 4 tablets. In some patients, presumably those with true pre-eclampsia, the sodium ion, especially as sodium chloride, caused a definite increase in the weekly gain in weight, in the degree of edema, in the blood pressure, and in the proteinuria. However, in about 70 per cent of the patients there was no difference in the response to any of the four substances used.

These studies of the oral and intravenous injection of sodium salts indicate that many patients who have signs of toxemia do not have true pre-eclampsia. We suggest the term "pseudo pre-eclampsia."

It is a waste of time to restrict the sodium intake of patients with pseudo pre-eclampsia as well as of many patients with hypertensive disease. Our work indicates a need for a better selection of patients and a more rigid restriction of the sodium ion in patients with true pre-eclampsia.

References

Darrow, D., and Pratt, E.: J. A. M. A. 143: 365, 1950.

Dexter, L., and Weiss, S.: Preeclamptic and Eclamptic Toxemia of Pregnancy, Boston, 1941, Little Brown and Co.

Dieckmann, Wm. J.: The Toxemias of Pregnancy, St. Louis, 1941, The C. V. Mosby Company.

Dieckmann, Wm. J., Seski, A. G., McCartney, C. P., Smitter, R. C., Pottinger, R. E., Brunetti, R., Rynkiewicz, L. M., Allen J. and Regester, R: Am. J. Obst. & Gynec., 58: 1014, 1949.

Dieckmann, Wm. J.: Toxaemias of Pregnancy (Human and Veterinary), A Ciba Foundation Symposium, London, 1950, J. & A. Churchill, Ltd.

Drury, A., and Jones, N.: Heart 14: 55, 1927.

DIABETES IN PREGNANCY

ROBERT E. HALL, M.D., AND ALVIN J. B. TILLMAN, M.D., NEW YORK, N. Y.

(From the Sloane Hospital for Women and the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University)

THE purpose of this paper is to report the observations made upon the pregnant diabetics seen at the Sloane Hospital for Women since the advent of insulin, and to record the conclusions reached from this experience.

The original data for this work were culled from the files of the Sloane Hospital between January, 1923, and September, 1949. During these post-insulin years at this hospital there were 112 diabetic patients, with 147 pregnancies, 97 of which were on the ward service and 50 on the private service.

Maternal Considerations

Incidence.—Our incidence of diabetes in pregnancy was represented by a ratio of 1:480 during the 27 years studied. This figure is surprisingly close to the Metropolitan Life Insurance Company estimate of slightly less than two diabetics per 1,000 during the childbearing age.[14] The similarity of these figures is by itself a gross means of emphasizing the virtually normal fertility rate encountered among treated diabetics.

Maternal Mortality.—Only one of our 147 pregnancies terminated in a maternal death. This was the case of a 37-year-old primigravida with severe diabetes, arteriosclerosis, and a blood pressure in the range of 215/140. She died of a cerebral hemorrhage 16 hours after a hysterotomy and sterilization were performed during the eleventh week of gestation.

Antenatal Care.—Because of the variability in glucose tolerance encountered in the pregnant state and because of the high fetal mortality associated with even the mildest cases, which might have been clinically occult in the nonpregnant state, early recognition and meticulous control of the diabetes comprise the most vital elements of therapy. It is imperative, for these reasons, that the patient be seen from the very beginning of her pregnancy; five of our fetuses were lost because the mothers failed to report until they were in acidosis. Although it is doubtful that pregnancy is an inciting cause of diabetes, early cases are often detected in the antenatal period; 22 per cent of our cases were discovered at this time. Once the diagnosis is established, the patient and the doctor must work with concerted vigilance to attain a calorie-insulin ratio which will prevent acidosis and allow for nutrition of mother and fetus without excessive weight gain. Because the lactosuria and lowered renal threshold of later pregnancy render urinalysis less reliable, the Benedict test must be frequently checked by simultaneous blood sugar determinations. Patients must be hospitalized for the slightest evidence of acidosis or toxemia.

Insulin Requirement.—It is generally agreed[4, 5, 10, 11, 12, 17, 19] that an individual diabetic patient's insulin requirement is unpredictable, but that it does tend to increase as pregnancy advances. Among our patients reaching the

third trimester, there were 18 who required no insulin whatsoever; of the remaining 86, only three did not require increments to their original doses. This change in glucose tolerance was always insidious and likely to occur in any trimester or all three, but most often in the first and last.

It is well known that glucose tolerance is regained immediately post partum. Because of this we routinely cut our insulin dosage in half the day after delivery in order to prevent the hypoglycemic reactions that would otherwise inevitably follow. Thus we have learned to interpret the increased insulin requirement of the pregnant diabetic as evidence of a temporary increase in metabolic function rather than the manifestation of a permanent alteration in the severity of the disease. When the insulin demands in the pre- and post-pregnancy states are compared, a significant increase is rarely encountered. As a matter of fact, of the 15 of our patients who had required more than 40 units of insulin before pregnancy, 13 were found to be well controlled by less than their original dose when seen one month post partum. The ultimate effect of pregnancy on diabetes is therefore negligible.

Fetal Mortality

It is, of course, the unexplained fetal mortality of 30 to 40 per cent, as it is generally known, that points to our basic ignorance of this disease and piques our interest in studying it. Excluding our 12 early spontaneous and 28 therapeutic abortions, we have had 107 pregnancies with 22 fetal deaths, making our gross fetal mortality 20.7 per cent. Further elimination of our 3 late abortions makes our mortality 18.3 per cent among our 104 viable births. This analysis is represented in Table I.

TABLE I. OUTCOME OF 147 PREGNANCIES AT SLOANE HOSPITAL

	NO. OF CASES	PERCENTAGE OF TOTAL CASES	PERCENTAGE OF VIABLE BIRTHS
Previable (43 Cases = 29%).—			
Therapeutic abortions	28	19.0	
Spontaneous early abortions (1-14 weeks)	12	8.2	
Spontaneous late abortions (15-27 weeks)	3	2.0	
Viable (104 Cases = 71%).—			
Term infants, living (38 weeks or more)	56	38.1	53.9
Premature infants, living (28-37 weeks)	29	19.7	27.9
Premature infants who died in the neonatal period	2	1.4	1.9
Macerated stillborn infants	12	8.2	11.5
Nonmacerated stillborn infants	5	3.4	4.8
Totals	147	100.0	100.0
Fetal Mortality.—			
Excluding therapeutic abortions			$\frac{34}{119} = 29\%$
Excluding therapeutic and early abortions			$\frac{22}{107} = 20\%$
Excluding therapeutic, early, and late abortions			$\frac{19}{104} = 18\%$

The 22 fetal losses included 3 late abortions, 12 macerated stillborn infants, 5 nonmacerated stillborn infants, and 2 neonatal deaths. These cases are listed in Table II together with the complications associated with them. Two of the 3 patients with late abortions were in acidosis when first seen at the hospital, and the third appeared for only one antepartum visit at the

TABLE II. FACTORS ASSOCIATED WITH FETAL DEATHS

PROBABLE CAUSE OF DEATH	NATURE OF FETAL DEATH	
Antepartum neglect of diabetes and fibroids	Late abortion	Fibroids; aborted nine days after first seen (26 weeks)
Acidosis	Late abortion	In acidosis when first seen; aborted two days later (26 weeks)
Acidosis	Late abortion	Careless with diet; acidosis and fetal death in twenty-seventh week
Antepartum neglect of diabetes; toxemia	Macerated stillborn infant	Mild hypertensive toxemia; no insulin therapy; fetal death in thirty-ninth week
Toxemia	Macerated stillborn infant	Mild pre-eclampsia at thirty-fourth week; fetal death in thirty-fifth week
Toxemia	Macerated stillborn infant	Mild pre-eclampsia at thirty-fifth week; fetal death in thirty-seventh week
Acidosis	Macerated stillborn infant	Private case with no antepartum record; acidosis in eighth month
Antepartum neglect of diabetes	Macerated stillborn infant	Patient left the city during her last month; returned with glycosuria and with fetus dead in utero
Toxemia	Macerated stillborn infant	Mild hypertensive toxemia at 32 weeks; fetal death at thirty-seventh week
Hypertensive cardiovascular disease; toxemia	Macerated stillborn infant	43-year-old with severe (180/95) hypertension throughout pregnancy; fetus died in twenty-eighth week
Antepartum neglect of diabetes	Macerated stillborn infant	Year 1924; diabetes diagnosed post partum
Acidosis	Macerated stillborn infant	Vomiting with acidosis and death in utero at 34 weeks; delivered elsewhere
Toxemia	Macerated stillborn infant	40-year-old habitual aborter; oral stilbestrol therapy throughout pregnancy; moderate pre-eclampsia at 26 weeks; fetal death at 30 weeks
Antepartum neglect of diabetes and toxemia	Macerated stillborn infant	Diabetes diagnosed in third trimester; moderate hypertensive toxemia with fetal death at 40 weeks
Antepartum neglect of diabetes	Macerated stillborn infant	Private case with no antepartum notes; fetus died in thirty-ninth week; another stillbirth elsewhere due to acidosis two years later
Obstetrical complication	Nonmacerated stillborn infant	No toxemia; abruptio placentae at 34 weeks
Obstetrical complication	Nonmacerated stillborn infant	4,100 gram baby; multiple failed forceps and ultimate craniotomy
Antepartum neglect of diabetes; premature delivery	Nonmacerated stillborn infant	First seen at delivery of 1,490 gram infant in breech presentation; fetal heartbeat disappeared in labor
Antepartum neglect of diabetes and obstetrical complication	Nonmacerated stillborn infant	No antepartum care; postpartum coma; arrived in labor room with prolapsed cord
Antepartum neglect of diabetes and premature delivery	Nonmacerated stillborn infant	No antepartum notes; delivered 1,900 gram premature stillborn infant at 32 weeks
Premature delivery; obstetrical complication	Neonatal death	1,330 gram premature (35 weeks) delivered with cord tightly around neck two times; died in nine hours of prematurity and brain hemorrhage
Antepartum neglect of diabetes; premature delivery	Neonatal death	Year 1927, uncooperative, poor antepartum care; delivered in thirty-first week of a 1,650 gram premature infant that died the same day

twenty-fourth week when she was found to have fibroids, and she aborted only nine days later. Of the 12 macerated stillborn infants, 3 were associated with acidosis and 7 with toxemia; only 4 of these 12 mothers had adequate antenatal care of their diabetes. As for the 5 stillbirths of nonmacerated infants one was the result of abruptio placentae at the thirty-fourth week (not associated with toxemia); one was an intrapartal death due to multiple failed forceps and eventual craniotomy on a large baby; and of the other 3, none of which had any antenatal care, 2 died of prematurity and one arrived in the labor room with a prolapsed cord. And, finally, there were 2 neonatal deaths, both of premature infants (both under 1,700 grams), one with the cord tight around the neck at delivery, and the other with no antepartum care.

Antepartum Care.—From analyses of these 22 fetal deaths in the light of the adequacy of antenatal care given the mother, it was concluded that 14 of them were associated with insufficient supervision. Ten of the 14 mothers were not seen in the clinic before they reached the third trimester, and the other 4 failed either in keeping their appointments or in adhering to their dietary instructions. Exclusion of these inadequately treated cases would give us the highly corrected fetal mortality of 8.6 per cent. The only satisfaction we can derive from such an artificial calculation is the knowledge that such a figure might be achieved with full cooperation of the patient if she registered early in every case. It also helps to illustrate, in theory, that careful regulation of her diabetes alone can assure the diabetic practically the same fetal risk as the nondiabetic, and, conversely, that poor control can kill the fetus.

This factor of close antenatal supervision is an important one in considering Priscilla White's results, for she sees most of her patients weekly throughout their pregnancies.[21, 25] As a matter of fact, she reported having seen her first 125 patients "almost daily during the third trimester of pregnancy."[24]

For the past 15 years, White's fetal mortality is 18 per cent of 439 viable births[22]; for the past 27 years, our fetal mortality is 18 per cent of 104 viable births.

White's series included 89 cases with abnormal hormone values and a fetal mortality of 42 per cent, 297 with "corrected" hormone values and a fetal mortality of 11 per cent, and 47 with normal values and a fetal mortality of 5 per cent.[23] These figures exclude one case of placenta previa, 4 cases of premature rupture of the membranes, and one case of erythroblastosis. Most of these patients were seen weekly after the diagnosis of pregnancy was made.

If we should exclude the 12 patients with viable infants in our series who received inadequate antepartum care, we would have a fetal mortality of 7.6 per cent. Further excluding our case of abruptio placentae, the fetal mortality would be 6.6 per cent. Hypothetical as this sort of reasoning is, it does offer an alternative explanation to White's excellent results.

Causes of Fetal Death.—In realistic deference to the fact that no random group of patients can be seen under ideal circumstances, it is important to analyze our mortality figures with respect to the complications associated with them and the means we have of protecting the fetus from these hazards. Among the factors held responsible for these fetal deaths, the following are most often mentioned in the literature: (1) spontaneous abortion, (2) hydramnios, (3) congenital deformities, (4) acidosis, (5) hypoglycemia, (6) toxemia, (7) prematurity, and (8) big babies. It seems that in the early days of the insulin era, almost every obstetrical accident was thought to occur with greater frequency in diabetics. Because of the persistent emphasis on some of these complications, each deserves separate consideration, but only the perspective gained through experience has enabled us to ascribe to each its particular significance.

1. Spontaneous Abortion.—Until recently it was generally believed that diabetics are prone to early abortions. The spontaneous abortions in our series numbered 12, or 9.4 per cent, before the fourteenth week, and 3, or 2.5 per cent, between the fourteenth and twenty-eighth weeks. During the same twenty-seven-year interval, our total (early and late) abortion rate among nondiabetics was 9.2 per cent. The factor of acidosis alone seems capable of creating a difference between the incidence of abortions among diabetics and nondiabetics. Two of our 12 early and 2 of our 3 late abortions could be attributed to this complication. Correcting our figures for this one circumstance would render our early and late abortion rates 7.7 and 0.8 per cent, respectively. It therefore seems reasonable to conclude that the carefully controlled diabetic aborts no more frequently than the nondiabetic.

2. Hydramnios.—Another complication of debatable importance is the frequent occurrence of hydramnios. In our series, hydramnios was recorded in 10, or 9.6 per cent, of the 104 pregnancies reaching the third trimester. It is believed highly probable that in many other cases the amnionic fluid was excessive but not sufficiently appreciated to prompt the diagnosis of hydramnios. The diabetic control of our patients with this diagnosis did not differ appreciably from that of the other cases.

3. Congenital Abnormalities.—Diabetic babies have been scrutinized for congenital abnormalities ever since Lecorche[13] in 1885 reported two with hydrocephalus. White[19] and others believe that such deformities are more likely to result from diabetic pregnancies. She has reported an incidence noted at birth of 1 : 8, compared with the expected ratio of 1 : 85.[21] Among our 104 babies, not a single deformity was found. Although conclusions from so small a series are likely to be erroneous, as with the abortion question, it does seem a little implausible to attribute any great significance to such rare complications. No one has tried to explain why diabetics should have congenitally abnormal progeny.

4. Acidosis.—In 1943, Priscilla White wrote that "acidosis per se is not important as a lethal factor in producing fetal death."[24] Prior to that ketosis had been consistently regarded as the most feared complication of a diabetic pregnancy. Our experience dramatically illustrates the validity of this latter view.

Acidosis was encountered in 9 cases of our series. In 3 it was mild, with the carbon dioxide combining power in each instance above 20 volumes per cent, and none of these babies were affected. Six patients, however, developed severe acidosis, without coma, but with carbon dioxide values of less than 20 volumes per cent, and the fetus died in each case. There were 4 abortions, at 14, 16, 26, and 27 weeks, and 2 macerated stillborn infants, at 34 and 38 weeks. The episode of acidosis was followed in each case by fetal death or abortion within a few days. In 5 of the 6 fatal cases acidosis was present when the patient was first seen (i.e., they received no antenatal care), and the sixth was a private patient who did not adhere to her diet. In 4 of these 6, the acidosis was precipitated by vomiting.

In addition to these cases of proved acidosis, at least 9 others were associated with such blatent neglect of their diabetes that subclinical acidosis becomes a possible explanation of their fetal losses. Since the fetus is so sensitive to temporary alterations in the maternal pH, it is not unlikely that this mechanism explains many cases of premature delivery and death in utero.

Ketosis is known to occur more frequently in pregnancy and its occurrence can certainly kill the fetus. These facts alone should emphasize the importance of careful regulation of the pregnant diabetic patient.

5. Hypoglycemia.—Hypoglycemia, on the other hand, does not seem so harmful to the fetus. The subjective sensations associated with low blood

sugar levels were recorded in varying degree in 19 cases. Three of the patients were hospitalized in hypoglycemic shock, 2 in the first and one in the last trimester. Two of these patients gave birth to living children and one underwent a therapeutic abortion. The other 16 were similarly unaffected.

It is pertinent in this connection to mention a nondiabetic private patient who received twenty courses of insulin shock therapy for schizophrenia during the fourth to seventh months of her pregnancy and yet proceeded to deliver a normal living child at term.

6. Toxemia.—The incidence of toxemia in diabetics as reported in the literature has varied from 9 per cent[12] to 50 per cent.[18] White claims that it is 50 times more common than in the nondiabetic. Evidence of toxemia* was noted in 34, or 32 per cent, of our cases, or a little more than twice our control figure. Sixteen were classified as pre-eclamptic and 18 as hypertensive; none had convulsions. This increased frequency of toxemia in diabetics is not surprising in light of the common knowledge that diabetics are prone to vascular disease[2] and, in turn, toxemia is more likely to involve a previously damaged vascular system.

Among our 34 cases of toxemia, the fetal mortality was 24 per cent. It was 19 per cent among the 73 comparable cases without toxemia. The duration of the toxemia varied from one to thirteen weeks and was no different in the fatal cases. Although toxemia was observed in 8 of our cases of fetal loss, it was regarded as the sole cause of death in only 3. Two of these 3 mothers were severe juvenile diabetics; one had been diabetic for 10 and the other for 22 years. White had shown that this type of patient is the most likely of all to develop toxemia with fetal death.[20]

It is impossible to deduce from our series whether or not toxemia per se entails any greater risk to the young diabetic than to the nondiabetic. It does seem undeniable, however, that the incidence of both toxemia and fetal death increases unavoidably in cases of long-standing diabetes, where arteriosclerotic changes are invariably present.

7. Prematurity.—There is little doubt that diabetics are prone to deliver prematurely. Thirty-six per cent of our live infants were born before the thirty-eighth week. The mechanism of premature labor in these cases may be concerned with the overdistention of the uterus by big babies; and because of this greater fetal size, it is impossible to define prematurity on the basis of birth weight. In this respect only 9, or 8.7 per cent, of our babies were premature, i.e., under 2,500 grams, as opposed to 7.5 per cent in nondiabetic pregnancies.

Whereas many of our fetal losses were associated with premature delivery or death in utero, there was usually some other complication such as acidosis which could be held as the lethal factor. In only 4 cases could prematurity be considered the primary cause of death, and 3 of these were associated with complete antepartum neglect. Perhaps prematurity plays an important role in the fetal mortality in diabetic patients only when the diabetes is poorly controlled.

8. Large Babies.—That the offspring of diabetics tend to be larger than normal is almost undisputed today. As pointed out by Herrick and Tillman,[8] this finding is inconsistent among individual cases, for some of the babies are actually underweight; but the general tendency is quite plain. White has shown that the chance of a diabetic producing an oversized infant is 8 in 10. Our figures show the average birth weight to be 3,587 grams (7 pounds, 14 ounces) at the thirty-eighth week, and 3,856 grams (8 pounds, 8 ounces), 4,137

*A diagnosis of toxemia is made at Sloane Hospital if three blood pressure readings of 130/90 are recorded in the patient's antepartum course.

grams (9 pounds, 2 ounces), and 4,153 grams (9 pounds, 3 ounces) at the thirty-ninth, fortieth, and forty-first weeks, respectively. Of the 58 of our infants born at term, only 9 weighed less than 7 pounds, whereas 36 weighed more than 8 pounds. This fetal enormity alone was responsible for one fetal death, 8 cases of impacted shoulders, 2 fractured humeri, and a midforceps rate of 13 per cent. It seemed to have little appreciable effect on the length of labor.

The Mode of Delivery

Cesarean Section.—The mode of delivery is an important consideration in the intelligent management of the diabetic parturient. The main issue is whether or not to do elective cesarean sections. Priscilla White has been the greatest champion of almost routine surgical interference. Before her endocrine studies she advocated cesarean sections to prevent "death and decay of the over-ripe fetus."[19] Now that she is able to prevent toxemia and control the birth weight by endocrine therapy, she still has a section rate of 75 per cent.[21, 25]

A number of obstetrical services have followed this policy; an equal number have adamantly rejected it. Herrick and Tillman,[8] in 1937, decried the increased infant mortality incurred by the interruption of pregnancy before term, an objection which gains validity from the fact that more than half of White's fetal deaths occurred in the neonatal period (as opposed to only 10 per cent in our series).

The section rate for diabetics at Sloane Hospital has been 16 per cent, and, with few exceptions, these were all performed at term for purely obstetrical indications. If, like Priscilla White, we had sectioned 75 per cent of our patients reaching the thirty-seventh week, we would have done about 50 additional sections, with a maximum theoretical salvage of 5 more babies.

Whereas it does seem reasonable to elect operative interference more liberally in individual diabetics with refractory toxemia or a history of stillbirth, there is as yet no conclusive evidence to support this mode of delivery as a routine procedure.

Induction of Labor.—The induction of labor in diabetics seems to be a more sensible means of preventing any last-minute fetal death in utero. Since it is rarely feasible much before term, it should provide assurance against the delivery of a premature infant. Labor was successfully induced in 18, or 17 per cent, of our cases, but only once before the thirty-eighth week.

Sterilization.—Sterilization has a distinct place in the treatment of these patients, especially after two or more successful pregnancies. The conventional rationale revolves about the prevention of further vascular damage in these women who have an already shortened life expectancy. It also helps to limit inheritance of the disease. Nineteen of our 112 patients were sterilized, 10 during therapeutic abortions, 8 in the course of cesarean section, and one in the puerperium.

Therapeutic Abortion.—Twenty-eight, or 19 per cent, of our patients underwent therapeutic abortion. Although, in the light of present standards, this rate seems rather high, many of these cases were seen during the early days of insulin therapy. Perhaps this practice accounts in part for our relatively low mortality figures. In most cases, diabetes alone does not justify the interruption of a pregnancy, for the maternal mortality is virtually unaffected, and any change in the severity of the disease is transient and self-limited. Only if the diabetes is unusually severe, long-standing, or associated with such other complications as vascular disease is abortion indicated. Under such conditions the risk to both mother and fetus is irrefutably enhanced.

Summary and Conclusions

1. An analysis has been made of the cases of diabetes in pregnancy seen at the Sloane Hospital since the advent of insulin therapy. The material consists of 112 patients, providing 147 pregnancies.

2. Maternal Considerations: Diabetes was found in one out of every 480 pregnancies. There was one maternal death which occurred in a patient with severe hypertension. In our experience, the most vital prerequisites to a successful outcome in these cases are the early diagnosis and meticulous supervision of the diabetes. Changes in glucose tolerance may be sudden or insidious; unrecognized or inadequately treated, these changes may result in fetal death.

3. Fetal Mortality: With the exclusion of our 12 early spontaneous and 28 therapeutic abortions, the gross fetal mortality is 20.7 per cent. Further excluding the 3 late abortions reduces it to 18.3 per cent among the 104 viable births. In analyzing the causes of fetal loss, inadequate antenatal care was thought to be the factor most often responsible; exclusion of the inadequately treated cases would lower our mortality to 7.6 per cent of the viable births.

Acidosis alone killed the fetus in 6 cases. Toxemia, observed in 32 per cent of the patients, was associated with 8 fetal fatalities, but was regarded as the sole cause of death in only 3; two of these occurred in patients who were severe juvenile diabetics. Premature delivery was found also to play a role in the fetal mortality, especially in cases with poor diabetic control. Big babies were a minor factor; hydramnios, congenital deformities, and abortions per se were thought to be of negligible significance.

4. Mode of Delivery: Sixteen per cent of the patients underwent cesarean section. Although this means of delivery was considered more freely in cases of previous stillbirth or refractory toxemia, its routine use is thought to result in more neonatal deaths than fetuses saved from death in utero. Induction of labor is recommended. Sterilization and therapeutic abortion serve a distinct, though circumscribed, function in the management of these cases.

References

1. Barns, H. H. F., and Morgans, M. E.: J. Obst. & Gynaec. Brit. Emp. **55**: 449, 1948.
2. Dolger, H.: J. A. M. A. **134**: 1289, 1947.
3. Dolger, H., and Herzstein, J.: Letter to Editor, J. A. M. A. **125**: 931, 1944.
4. Duncan, G. G., and Fetter, F.: Am. J. M. Sc. **187**: 347, 1934.
5. Eastman, N. J.: Obst. & Gynec. Surv. **1**: 3, 1946.
6. Gaspar, J. L.: West. J. Surg. **53**: 21, 1945.
7. Gilbert, J. A. L., and Dunlop, D. M.: Brit. M. J. **1**: 48, 1949.
8. Herrick, W. W., and Tillman, A. J. B.: Surg., Gynec. & Obst. **66**: 37, 1938.
9. Herzstein, J., and Dolger, H.: Am. J. Obst. & Gynec. **51**: 420, 1946.
10. Hurwitz, D., and Irving, F. C.: Am. J. M. Sc. **194**: 85, 1937.
11. Lavietes, P. H., Leary, D. C., Winkler, A. W., and Peters, J. P.: Yale J. Biol. & Med. **16**: 151, 1943.
12. Lawrence, R. D., and Oakley, W.: Quart J. Med. **11**: 45, 1942.
13. Lecorche: Ann. de gynéc. **24 (2)**: 257, 1885.
14. Marks, H. H.: M. Clin. North America **31**: 369, 1947.
15. Miller, H. C.: New England J. Med. **233**: 376, 1945.
16. Miller, H. C., Hurwitz, D., and Kuder, K.: J. A. M. A. **124**: 271, 1944.
17. Peckham, C. H.: Bull. Johns Hopkins Hosp. **49**: 184, 1931.
18. Potter, E. L., and Adair, F. L.: Am. J. Obst. & Gynec. **35**: 256, 1938.

19. White, P.: Surg., Gynec. & Obst. 61: 324, 1935.
20. White, P.: M. Clin. North America 31: 395, 1947.
21. White, P.: Proc. Third American Congress on Obstetrics and Gynecology, 1947, p. 223.
22. White, P.: Am. J. Med. 7: 609, 1949.
23. White, P.: Am. J. Obst. & Gynec. 33: 380, 1937.
24. White, P., and Hunt, H.: J. Clin. Endocrinol. 3: 500, 1943.
25. White, P.: Personal communication.

620 West 168th Street

THE CAUSE OF THE BLOOD COAGULATION DEFECT FOLLOWING ABRUPTIO PLACENTAE*†

ERNEST W. PAGE, M.D., LEE D. FULTON, M.D., AND
MARY BETH GLENDENING, PH.D., SAN FRANCISCO, CALIF.

(From the Division of Obstetrics and Gynecology, University of California School of Medicine)

THE occurrence of a failure in the blood clotting mechanism following certain severe cases of abruptio placentae has been recognized for a considerable period of time. Though uncommon, this coagulation defect becomes a major factor in those maternal deaths which result from a premature separation of the placenta.

DeLee, who was called in 1901 to attend a case of abruptio placentae with uncontrollable hemorrhage, made the observation that the patient's blood failed to clot even after several days, and he described the condition as a "temporary hemophilia."[1] In 1915, Williams[2] reported a case in which placental separation was followed by a fatal hemorrhage due to a failure of the clotting mechanism. He thought the blood was like that of persons who were victims of certain types of snake bites. In 1922, Willson[3] presented a paper on abruption of the placenta, and described 14 deaths from continued hemorrhage out of a series of 69 collected cases. He proposed the hypothesis that the placenta was the source of some toxic material which he called a "hemorrhagin" and which gained entry into the maternal circulation to produce the clotting defect. Kellogg,[4] in reporting an autopsy on such a case in 1928, was impressed by the extensive hemorrhage into all organs as well as the inability of the blood to clot. He amplified this series considerably in 1945.[5]

The nature of this hemorrhagic phenomenon was not investigated systematically until recently. The first demonstration of the nature of the defect was made by Dieckmann[6] in 1936, who found significantly reduced levels of blood fibrinogen in patients who hemorrhaged following abruptio placentae. He noted similar depletions of fibrinogen in fatal cases of eclampsia,[7] which suggests that some common denominator might be operating to produce this defibrination in both conditions. The clinical association of abruptio with toxemia, of course, has been long recognized.

A separate line of investigation, concerned initially with the toxicity of placental extracts, subsequently became associated with this problem. In 1919, Obata[8] noted that aqueous placental extracts given intravenously to rabbits produced at first a hastening of blood coagulation and later a delay. This was confirmed by Hori and Sakurai.[9] Pursuing this further, Schneider[10] identified the toxic principle as thromboplastin, and confirmed Obata's observation that those animals which survived a sublethal dose of placental extract became totally refractory to lethal doses. Fulton and Page[11] found that this refractory state was due to the depletion of fibrinogen. Based upon this, one of us suggested, in discussing Kellogg's paper on the hemorrhagic syndrome following abruptio,[12] that the coagulation defect was caused by defibrination resulting from the escape

---

*Presented before the Pacific Coast Obstetrical and Gynecological Society Nov. 1, 1950.

†This work was supported in part by grants from the Christine Breon Fund and from the American Foundation for High Blood Pressure.

of placental thromboplastin into the maternal circulation. Schneider[13] produced abruptio placentae experimentally in rabbits by traumatizing the placental site, and noted visceral lesions which he attributed to the native extraction of thromboplastin by maternal blood bathing the area of tissue injury, but he did not observe an endogenously produced coagulation defect.

A still different line of investigation has a bearing on the etiology of this hemorrhagic syndrome. Smith and Smith[14] noted the presence of fibrinolytic activity of the blood serum in cases of pregnancy toxemia. This led a number of workers to believe that the disappearance of fibrinogen is due to its lysis by the fibrinolytic enzyme (plasmin) which normally exists in human plasma as an inactive precursor (plasminogen). Moloney, Egan, and Gorman[15] reported a case of abruptio with afibrinogenemia which was successfully treated by the administration of human fibrinogen. They attributed the syndrome to the action of a fibrinolytic enzyme, as did Weiner, Reid, and Roby[16] who found increased activity of fibrinolysin in the plasma of women with severe placental separation. They also treated the syndrome successfully with human fibrinogen.

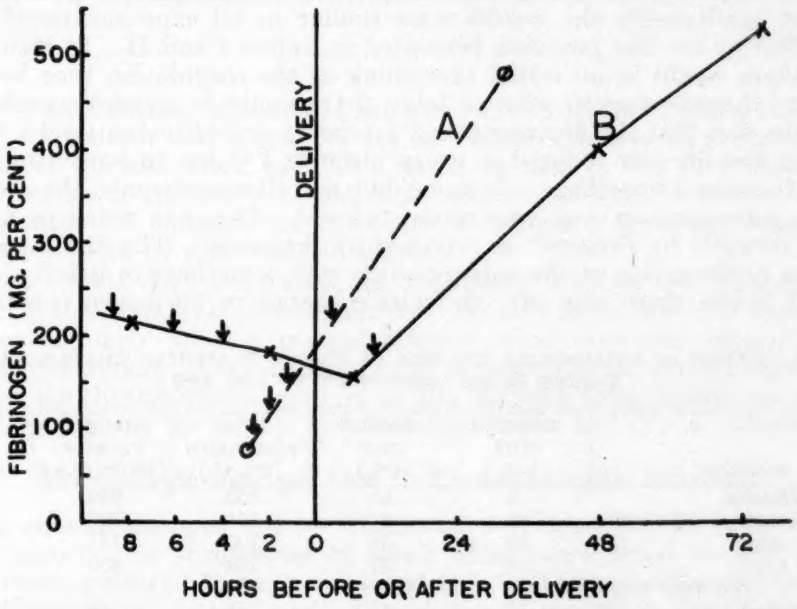


Fig. 1.—Plasma fibrinogen levels in two cases of severe abruptio placentae. Each arrow indicates a transfusion of 500 c.c. of whole blood.

Clinical Observations

Our own data with respect to fibrinogen concentrations are limited to six cases, three of which were mild degrees of separation showing plasma levels of fibrinogen within the normal range. The fourth was a fatal case, in which a toxemia with severe separation was followed by a hemorrhagic state and irreversible shock. Autopsy revealed a total infarction of the liver with numerous fibrin deposits in and around the blood vessels. The blood would not clot upon the addition of thrombin and the plasma contained no fibrinogen. The remaining two cases were severe placental separations, and even though no hemorrhagic state resulted (probably as the result of prompt and multiple transfusions), the fibrinogen concentrations were reduced almost to critical levels, as illustrated in Fig. 1. In none of these clinical cases did the undiluted plasma clot show evidence of lysis when placed in an incubator at 37° C. for 24 hours. (In the fatal case, a small amount of fibrinogen had to be added to form the clot.)

Reproduction of the Hemorrhagic Syndrome in Dogs

In 18 dogs, in vivo defibrination was produced by infusing slowly into the femoral vein a homogenized, aqueous extract of human placenta suspended in 5 per cent dextrose solution.* Before, during, and after the infusion—which commonly lasted from 30 to 120 minutes—observations were made on the clotting time (Lee-White technique), sedimentation rate, plasma fibrinogen concentration (method of Greenberg and Mirolubova[17] modified by the use of thrombin), and prothrombin concentration (by the two-stage method of Warner, Brinkhaus, and Smith[18]), both with and without added accelerator globulin in the form of beef serum. Plasma clots were placed in the incubator for observations of possible lysis. In addition, attempts were made to isolate and assay quantitatively the amounts of circulating thromboplastin, with the use of our own methods which will be described elsewhere. Biopsy specimens of the liver and kidney were obtained before and after the procedure.

There was some variability in the quantitative results from one animal to the next, depending upon the amount and the rate of thromboplastin administration, but qualitatively the results were similar in all experiments. They are exemplified by the two protocols presented in Tables I and II. In some experiments, there would be an initial shortening of the coagulation time because of the added thromboplastin; whereas later, there would be a sudden prolongation due to the fact that the fibrinogen had reached a critically low level. The prothrombin was likewise reduced in every instance, but not to concentrations low enough to cause hemorrhage. In some, but not all experiments, the accelerator globulin concentration was moderately reduced. This was noted in a clinical case of abruptio by Seegers[19] as reported by Schneider. The first event in our dogs was prolongation of the sedimentation rate, sometimes to infinity, and this occurred before there was any appreciable change in fibrinogen concentration.

TABLE I. EFFECT OF INTRAVENOUS INFUSION OF HUMAN PLACENTAL THROMBOPLASTIN ON VARIOUS BLOOD COMPONENTS OF DOG 6-50

SAMPLES	CLOTTING TIME (MIN.)	HEMATOCRIT (%)	FIBRINOGEN (MG. %)	THROMBOPLASTIN (UNITS/C.C.)	LYTIC ACTIVITY
Before infusion	3	39	352	986	0
15′ after start of infusion	4	43	304	346	0
30′ after start	10	38	190	148	0
45′ after start	9	37	164	450	0
Bleeding noted from all raw surfaces.					
70′ after start	10	42	81	46	0
75′ after start	No clot	42	0	47	0*
Infusion stopped. Amount given 1.26 million units in 450 c.c.					
15′ after stopping	No clot	41	0	—	0*
Bleeding from wounds continued, but dog recovered spontaneously.					

*Fibrinogen added to produce clotting before observation for lysis.

When the fibrinogen reached levels somewhat below 200 mg. per cent, the animals began to bleed continuously from their wounds, but usually recovered spontaneously and showed normal fibrinogen levels within one or two days. In two dogs (one of which is illustrated in Table II), the administration of 1.94 Gm. of human fibrinogen† intravenously resulted in a prompt cessation of the bleeding tendency. The course of events in these animals shows a remarkable resemblance to the timing and sequence of changes noted clinically, as in Case 3 of Weiner, Reid, and Roby.[16]

*These experiments were performed in collaboration with Dr. Richard Gardner and Dr. Orland Davies in the Division of Experimental Surgery, and will be reported in more detail in a separate communication. We are indebted to Jane O'Connell for all thromboplastin assays.

†The human fibrinogen was kindly supplied by Dr. W. E. Ward of Cutter Laboratories, Berkeley.

TABLE II. EFFECT OF INTRAVENOUS INFUSION OF HUMAN PLACENTAL THROMBOPLASTIN ON THE CLOTTING TIME, PROTHROMBIN, AND FIBRINOGEN OF DOG 13-50, AND INFLUENCE OF TREATMENT WITH FIBRINOGEN

	CLOTTING TIME	PROTHROMBIN (UNITS)	FIBRINOGEN (MG. %)
Control	2	120	405
Control (15′ later)	3		375
20′ after start of infusion	9	89	319
40′ after start	13		280
Oozing tendency noted.			
60′ after start	15	76	212
Marked hemorrhagic tendency.			
80′ after start	21		112
90′ after start	No clot	48	19
Thromboplastin infusion stopped after 1.76 million units. Infusion of human fibrinogen solution started.			
3′ later	No clot		72
30′ later	Poor clot	51	190
Bleeding tendency stopped. Fibrinogen solution discontinued.			
18 hours later	5	106	419
96 hours later	4	149	691

In ten experiments, the clotted samples were incubated (whole blood technique of Frommeyer and Epstein[20]) for several days, but in no experiment was any lysis of the clot observed. This could be due to the fact that human placental extracts contain a considerable amount of antifibrinolytic activity. The observations do indicate that the observed changes in the coagulation system were not produced by a fibrinolytic enzyme.

When female dogs were used, an indwelling catheter was placed in the bladder for observations of urinary output. As soon as the infusion was started, there was regularly noted a marked oliguria which persisted throughout the hours of observation. Very little, if any, thromboplastin was excreted in the urine, for the thromboplastic activity of the dialyzed urine before the infusion was just as high as the sample collected toward the end of the infusion.

Morphologic Changes Due to Thromboplastin Infusions

The visceral changes will be illustrated and described in more detail in another report. No thromboses of whole blood were noted in any animals, though there appeared to be a red blood cell "sludging" effect, especially in the small arterioles of the lungs. The glomeruli showed a broadening of the capillary wall, and fibrin deposits in and about the renal tubules. The liver showed fibrin thrombi in some of the capillaries, and scattered areas of necrosis.*

The Fate of Intravenous Placental Thromboplastin

There are several reasons why it would be of interest to determine what happens to thromboplastic proteins when they gain access to the blood stream. If it were possible, for example, to demonstrate with a microassay the quantity of placental thromboplastin in the circulating blood, it might be a useful tool to investigate some of these abnormalities of pregnancy. Our laboratory method can detect minute quantities added to blood in vitro then recovered by sedimenting the cellular elements with acacia and subjecting the plasma to high speed centrifugation.† When this method was applied to our dog experiments, we

*Since this article was prepared, extensive reviews of the possible role of thromboplastin in late obstetrical complications have been published by Schneider in the *Ciba Symposium on Toxemias of Pregnancy*, Philadelphia, 1950, The Blakiston Company, and in Surg., Gynec. & Obst. 92: 27, 1951.

†We are indebted to Dr. Walter Seegers, of Wayne University School of Medicine, for supplying several of the reagents used in this assay.

found that thromboplastic activity disappeared from the blood stream as rapidly as it was poured in. In fact, the total activity often appeared to be reduced (cf. Table I). Isolated organ perfusion indicated that the liver, the kidney, or the lung was not solely responsible for its disappearance.

When thromboplastin is added to blood in vitro, and fibrin is then removed by recalcification and rapid stirring with a rod, about 60 per cent of the added thromboplastin is removed along with the fibrin. Presumably, this is what happens within the animal, where the rapidly moving blood stream effectively defibrinates the blood, depositing the fibrin (together with thromboplastin) over a large surface. The fact that masses of fibrin are not encountered can be understood if we visualize in man a total of 25 Gm. of fibrin distributed in 60,000 miles of capillaries.

The question of the fate of the injected thromboplastin is being investigated further by the technique of tagging the molecule with radioactive iodine and studying its distribution in the various tissues of the rat. Such iodination does not interfere with the enzymatic properties of thromboplastin.

The Cause of Fibrinogen Disappearance Following Abruptio Placentae

There is no longer any doubt that the hemorrhagic state which occasionally follows severe cases of abruptio placentae is due to the depletion of fibrinogen. There are two current theories, however, as to the cause of this depletion; either the lysis of fibrinogen by a plasma fibrinolysin or our present thesis that it is due to the escape of placental or decidual thromboplastin into the maternal blood stream. We believe that the latter is the true explanation for the following reasons:

1. The syndrome may be reproduced, with all of the characteristic changes in the coagulation system of the blood, by the intravenous infusion of human placental thromboplastin.

2. The reduction of prothrombin, as well as accelerator globulin, after abruptio placentae can readily be explained—and reproduced—by intravenous thromboplastin, and cannot be explained by the action of fibrinolysin. It has been shown by Lewis, Howe, and Ferguson[21] that prothrombin is not lysed by this enzyme.

3. The lesions of the liver and kidney known to accompany abruptio placentae are best explained by the thromboplastin hypothesis, and can be reproduced by injections of thromboplastin, as demonstrated above, or produced endogenously as demonstrated by Schneider.[13]

4. The existence of fibrin thrombi, and the persistence of retroplacental clots containing fibrin, cannot be explained by the lysin theory inasmuch as fibrin is lysed by fibrinolysin just as readily as fibrinogen.

5. The rate of fibrinogen depletion in the clinical cases as well as in our dogs is measured in minutes, whereas the lysis of all blood fibrinogen by a plasma fibrinolysin would be exceedingly slow, based upon in vitro calculations.

6. None of our clinical cases, and none of our dogs defibrinated with thromboplastin, showed evidence of any fibrinolytic activity in the undiluted plasma.

7. There is doubt whether a high amount of fibrinolytic activity, such as is observed in vitro when plasma is treated in one of several ways, can actually exist in vivo. Whole blood contains a large amount of inhibitor to fibrinolysin, and at least two types of inhibitors, a heat-stable and a heat-labile inhibitor. As is true with almost every enzyme system found in blood, dilution reduces the inhibitor activity to a greater degree than the enzyme activity. Most of the demonstrations of lysin activity in human blood have depended upon dilution of the plasma; whereas, to be of physiologic significance, a high activity should

be demonstrated in undiluted blood. Other methods have relied upon a concentration of the enzyme, or a denaturation of inhibitor by treatment of plasma with chloroform, conditions which obviously do not prevail in the body. Ratnoff[22] has shown that the appearance of lytic activity in whole blood (observed after one or more days of incubation) is dependent upon a reduction of the inhibitor content rather than an increase in the amount of potential fibrinolysin present.

The reason for the existence of a fibrinolytic enzyme system in the blood is obscure, but the most reasonable explanation would be that it becomes activated *after* the occurrence of injury in order to remove any deposited fibrin slowly and repair the damage which was initiated by the action of thromboplastic proteins. This hypothesis is in keeping with clinical observations, and places the fibrinolytic enzyme system in the class of an adaptive mechanism responding to, but not resulting in an injury.

The logical treatment of the hemorrhagic syndrome following abruptio will hinge upon the availability of suitable preparations of human fibrinogen. This may be a difficult problem, because the hepatitis virus is often concentrated in this fraction, and the usual methods of irradiating plasma frequently denature the fibrinogen so that it becomes unstable. For the present, we must rely largely upon the use of blood or plasma, depending upon the relative need for red blood cells, but we must also realize that with severe fibrinogen depletion, many units may be required to restore the clotting power of the blood.

Summary

Abruptio placentae is sometimes followed by a hemorrhagic syndrome which results from a sudden depletion of plasma fibrinogen. This defibrination is probably due to the escape of placental or decidual thromboplastin into the maternal circulation. This converts prothrombin to thrombin, which in turn converts fibrinogen to fibrin, and the latter is deposited spottily over a very large vascular surface, sometimes producing serious visceral lesions.

The syndrome was reproduced in 18 dogs by the intravenous infusion of human placental thromboplastin. This resulted in fibrinolysin depletion, a variable reduction in prothrombin and accelerator globulin concentrations, an inability of the blood to clot, focal lesions in the liver and kidneys, and oliguria. All of these findings are sometimes encountered in severe cases of abruptio placentae. The administered thromboplastin disappeared almost immediately from the blood and was probably incorporated with the fibrin and fixed by the tissues.

No fibrinolytic activity was demonstrated in the undiluted plasma samples from 10 of the dogs in which the syndrome was produced nor in 5 clinical cases of abruptio placentae. Reasons are given for rejecting the hypothesis that an activation of a plasma fibrinolytic enzyme could account for the observed reductions of fibrinogen.

References

1. DeLee, J. B.: Am. J. Obst. & Gyneo. 44: 785, 1901.
2. Williams, J. W.: Surg., Gynec. & Obst. 21: 541, 1915.
3. Willson, P.: Surg., Gynec. & Obst. 34: 57, 1922.
4. Kellogg, F. S.: Am. J. Obst. & Gynec. 15: 357, 1928.
5. Kellogg, F. S.: Clinics 4: 585, 1945.
6. Dieckmann, W. J.: Am. J. Obst. & Gynec. 31: 734, 1936.
7. Dieckmann, W. J.: The Toxemias of Pregnancy, St. Louis, 1941, The C. V. Mosby Company.

8. Obata, I.: J. Immunol. 4: 111, 1919.
9. Hori, E., and Sakurai, K.: The Sei-I-Kwae M. J. 49: 16, 1930.
10. Schneider, C. L.: Am. J. Physiol. 149: 123, 1947.
11. Fulton, L. D., and Page, E. W.: Proc. Soc. Exper. Biol. & Med. 68: 594, 1948.
12. Kellogg, F. S.: Obst. & Gynec. Surv. 3: 746, 1948.
13. Schneider, C. L.: Surg., Gynec. & Obst. 90: 613, 1950.
14. Smith, O. W., and Smith, G. V. S.: Proc. Soc. Exper. Biol. & Med. 58: 116, 1945.
15. Moloney, W. C., Egan, W. J., and Gorman, A. J.: New England J. Med. 240: 596, 1949.
16. Weiner, A. E., Reid, D. E., and Roby, C. C.: Am. J. Obst. & Gynec. 60: 379, 1950.
17. Greenberg, D. M., and Mirolubova, T. N.: J. Lab. & Clin. Med. 21: 431, 1936.
18. Warner, E. D., Brinkhaus, K. M., and Smith, H. P.: Am. J. Physiol. 114: 667, 1936.
19. Seegers, W. H.: Proc. International & Fourth American Congress on Obst. & Gynec. 1950. In press.
20. Frommeyer, W. B., and Epstein, R. D.: New England J. Med. 241: 743, 1949.
21. Lewis, J. H., Howe, A. C., and Ferguson, J. H.: J. Clin. Investigation 28: 1507, 1949.
22. Ratnoff, O. D.: Bull. Johns Hopkins Hosp. 83: 29, 1949.

THE HISTIDINE CONTENT OF THE URINE IN PREGNANCY

GEORGE S. WELLS, PH.D., AND HOWARD B. LEWIS, PH.D., ANN ARBOR, MICH.

(From the Department of Biological Chemistry, Medical School, University of Michigan)

VOGE[1] in 1929 observed the presence of histidine in increased amounts in the urine of pregnancy and the close correlation of the Aschheim-Zondek test and the histidinuria. Kapeller-Adler[2, 3] in an extension of this work has urged the employment of the test for urinary histidine as a chemical diagnostic aid in pregnancy. Among others, Westberg[4] has studied this test carefully and has reported positive tests in 86 per cent of a large group (680) of pregnant women and in less than 3 per cent of 257 nonpregnant individuals (male and female). Page,[5] in a summary of the results of 21 investigators, states that in a total of 2,668 determinations in pregnancy, 2,205 (86 per cent) positive tests were obtained and that in 1,881 determinations with nonpregnant individuals. 1,659 (88 per cent) gave negative results.

Much of the difficulty in the study of the histidinuria of pregnancy has been associated with the accuracy and specificity of the method for the estimation of urinary histidine. The bromine reaction, first suggested by Knoop,[6] has been applied quantitatively by Kapeller-Adler[2, 3] and has been modified and used extensively by other workers in this field.[7-11]

Material

The present report is concerned with a careful study of the modified bromine reaction of Chattaway.[11] After the establishment of suitable conditions for the determination of histidine in the urine, we have examined 169 samples of urine from 100 pregnant women and 109 specimens from 108 subjects, both men and nonpregnant women. It has been possible to secure serial specimens of urine in a number of cases of pregnancy. Our results with the use of an improved method of histidine determination have indicated an increased excretion of histidine in pregnancy shown by a lowered urinary creatinine: histidine ratio. Although the number of urine specimens collected in the early months of pregnancy was limited, an increased excretion of histidine was not evident before the third month of pregnancy. The test would, accordingly, appear to be of limited value as an aid in the early diagnosis of pregnancy.

The specimens of pregnancy urine were, for the most part, made available to us through the cooperation of Dr. Norman Miller and Dr. T. N. Evans of the Department of Gynecology and Obstetrics of the Medical School and the University Hospital. We wish to express our special appreciation of the assistance of Mrs. Elaine A. Patterson, clinic nurse, without whose enthusiastic interest and practical cooperation, this study would have been impossible. The urines of nonpregnant individuals were collected from students in the classes of biological chemistry in this Department.

Since it was not possible to secure in every case complete 24-hour specimens of urine and since the dilution of random specimens of urine was variable, an attempt was made to secure a basis of evaluation and comparison of the results

obtained. For this purpose the creatinine:histidine ratio (Cr/H) was calculated (the ratio of milligrams of urinary creatinine per milliliter of urine to milligrams of urinary histidine per milliliter of urine). Since the excretion of creatinine is not altered significantly in pregnancy, it was believed that changes in this ratio might be significant as suggested by Langley.[9] A low ratio would thus be indicative of an increased excretion of urinary histidine.

Analytical Procedures

Creatinine.—Urinary creatinine was determined by the usual picric acid-sodium hydroxide procedure, the intensity of the color developed being measured by the use of the Klett-Summerson photoelectric colorimeter (green filter No. 54).

Histidine.—After many preliminary studies, the Chattaway modification[11] of the bromine test[6] was adopted with certain slight changes. In this procedure, an excess of bromine is allowed to react with histidine in an acid medium for 5 minutes at room temperature, the excess of bromine is removed by phenol, and the reaction mixture is heated in a boiling water bath in the dark for 5 minutes. The intensity of the brown color which develops is measured in the Klett-Summerson photoelectric colorimeter (purple filter No. 42). The histidine value, represented by the color developed, is calculated from a curve derived by the determination of known amounts of histidine under standard conditions, identical with those used for the unknown solutions. The relationship between the readings on the colorimeter and the concentrations of histidine was found to be represented by a straight line between the limits of 0.6 and 1.5 mg. of histidine. In subsequent work, volumes of urine which contained amounts of histidine within these limits were employed.

TABLE I. RECOVERY OF HISTIDINE ADDED TO SOLUTIONS CONTAINING UREA OR AMMONIUM SALTS

UREA OR AMMONIUM CHLORIDE (MG.)	HISTIDINE PRESENT (MG.)	HISTIDINE FOUND (MG.)	RECOVERED (PER CENT)
Series 1 (Urea).—			
0	0.8	0.790	99
2	0.8	0.660	82
2	0.8	0.690	86
2	1.0	0.810	81
2	1.6	1.285	80
4	1.0	0.645	64
4	1.6	0.960	60
Series 2 (NH_4Cl).—			
0	1.1	1.095	99
3.6	0.8	0.785	98
3.6	1.2	1.185	99
3.6	1.6	1.550	97
7.2	0.8	0.800	100
7.2	1.2	1.180	98
7.2	1.6	1.595	100

Chief among the substances present in urine, which influence the color development in the bromine reaction, is urea, in whose presence the color is depressed markedly.[9] If the histidine content of a urine specimen was determined and a known amount of histidine was added, it was possible to recover a part only of the added histidine. The influence of urea added to pure solutions of histidine is shown in Table I. Urea can be hydrolyzed to ammonium salts which do not interfere with the bromine reaction (Table I).

In subsequent work, the urinary urea was converted to ammonium salts by autoclaving with sulfuric acid. Histidine was not destroyed by autoclaving and histidine added to autoclaved urine could be recovered satisfactorily (96 to 109

per cent recovery). By this procedure, any peptides containing histidine (e.g., carnosine) are hydrolyzed, so the results obtained in our experiments represent *total* and not free histidine. Knoop[6] showed that no reaction with bromine was given by imidazolepropionic, imidazoleacetic, or imidazolecarbonic acids. We observed that neither imidazolelactic acid, imidazoleacrylic acid (urocanic acid), carnosine, nor ergothioneine, all present in tissues or formed in biological reactions, gives a color in the bromine reaction. Solutions of ergothioneine and carnosine were autoclaved with sulfuric acid as described for urine. Ergothioneine gave no color after autoclaving, but as expected, carnosine, a peptide containing histidine, was hydrolyzed and the histidine liberated could be determined quantitatively.

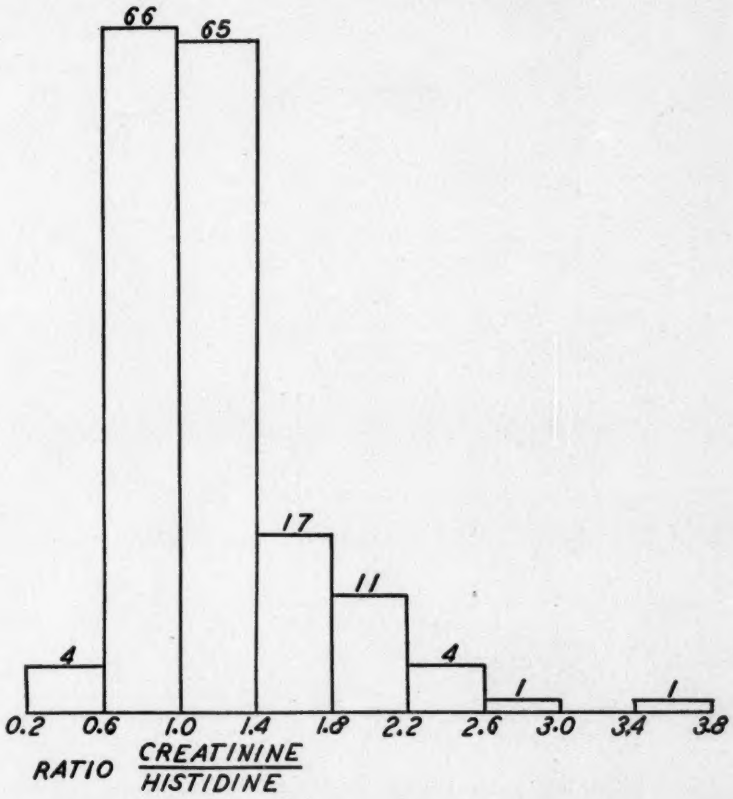


Fig. 1.—The distribution of the ratios of creatinine to histidine in 169 urines of pregnant women.

The procedure for the determination of histidine as finally adopted was as follows. Fifty ml. of urine were transferred to a 125 ml. Erlenmeyer flask, 6.4 ml. of sulfuric acid (a mixture of equal parts of concentrated acid and water) were added and 3.6 ml. of distilled water to make a total volume of 60 ml. The flask was stoppered with cotton and autoclaved for 5 hours at 15 pounds pressure. The autoclaved urine was cooled and filtered. One, 3, and 5 ml. of the autoclaved urine were introduced into a series of 3 tubes. After the color development, one tube at least will fall into the desired range. Dilute to 5 ml. with distilled water. The remainder of the determination is the same as that described by Chattaway,[11] except that since the urines as diluted are already acid due to the sulfuric acid used in the hydrolysis of urea, addition of acid is unnecessary.

In Table II is recorded a summary of the results obtained with all the urines examined. The samples of pregnancy urine were collected at various periods of gestation. The Cr/H ratios fell into two groups, those of the pregnant women and those of men and nonpregnant women, and there was little overlapping between the two groups. This is clearly shown in Figs. 1 and 2, in which the distribution of the ratios of urines of pregnant and nonpregnant individuals, respectively, is plotted. The abscissa represents the values of the ratio while the height of the columns shows the number of specimens which lay within a particular ratio grouping. For example, 66 of the specimens from pregnant women fell within the range of 0.6 to 1.0.

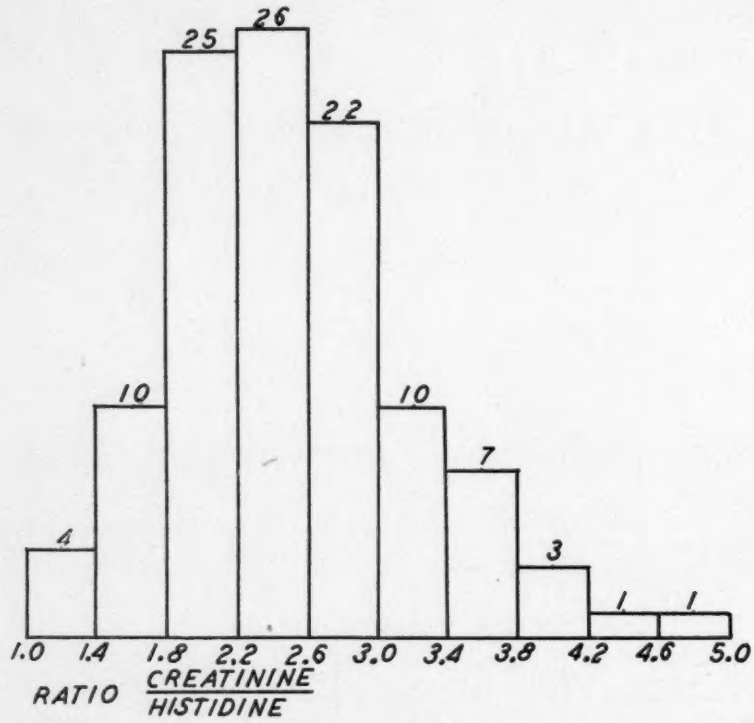


Fig. 2.—The distribution of the ratios of creatinine to histidine in the urines of 59 nonpregnant women and 50 men.

In the group of 50 samples of male urines examined were included 39 which comprised 24-hour specimens with an average daily excretion of histidine of 657 mg. Similarly, the average daily urinary histidine of 46 of the nonpregnant women was 494 mg. It was possible with subject W. C. F. to collect complete daily samples of urine monthly from the fourth to the ninth month of pregnancy and to obtain specimens of urine prior to pregnancy and after delivery. It will be noted that in contrast to the daily excretion of nonpregnant individuals, the histidine of the urine of this pregnant woman ranged from 1,120 to 1,690 with an average value of 1,430 mg. (Table III). After pregnancy, the Cr/H ratios which had ranged during pregnancy between 0.63 and 0.96 were comparable to those of nonpregnant women and men as presented in Table II.

An attempt was made to establish from the data an arbitrary Cr/H ratio which would divide the majority of the nonpregnancy urines from those of pregnancy. It may be seen from Figs. 1 and 2 that a ratio of 1.70 serves well in this respect. Eighty-eight per cent of the pregnancy urines and only 9

per cent of the nonpregnancy urines had ratios less than this value of 1.70. Such a correlation is similar to those of other workers, who have used different criteria of the histidinuria of pregnancy.

The distribution of the values of the Cr/H ratios in relation to the duration of pregnancy is shown in Fig. 3. Each point in the curve represents the average ratio of all the samples collected in the month of gestation indicated. The number of samples analyzed is shown by the numbers at each point of the curve. Although the average ratios of the relatively small number of urines secured early in pregnancy (1 to 2 months) approach the limiting value arbitrarily set in the present investigation as characteristic of urine of pregnancy, no conclusions can be drawn. However, a sharp drop was observed in the third month, an average

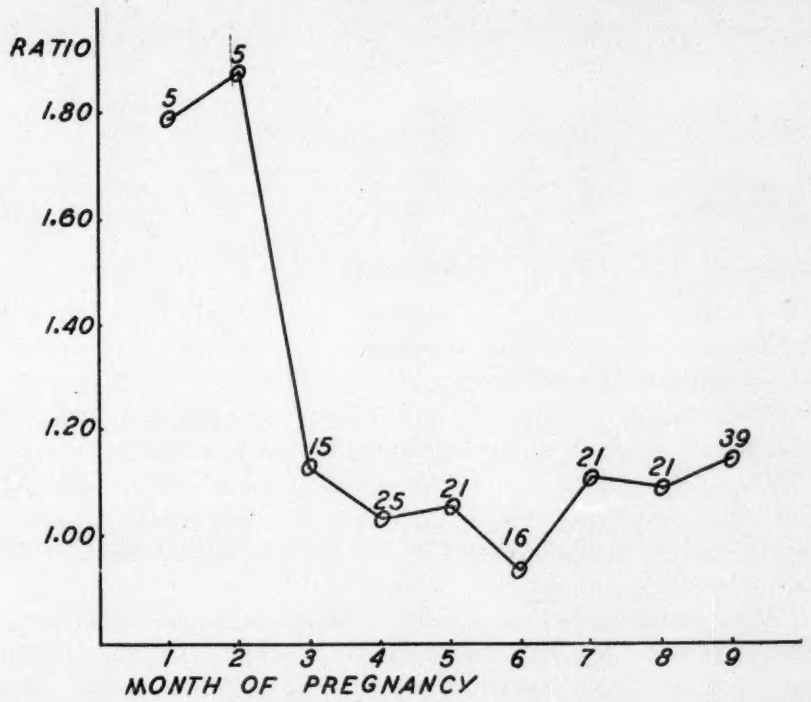


Fig. 3.—The distribution of the urinary creatinine:histidine ratios in relation to the period of gestation.

value being obtained which was maintained at a fairly constant level throughout the remainder of the period of pregnancy. It does not appear that the Cr/H ratio of the urine can be used for the diagnosis of early pregnancy, since, in our experience, the low ratios characteristic of pregnancy (Fig. 1) are not observed until after the second month of gestation. Our results also fail to show that the histidine excretion, as measured by the Cr/H ratio, is notably high at any particular period during pregnancy. This is in accord with the conclusion of Langley.[9]

There is no adequate explanation of the chemical or physiological basis of the well-established histidinuria of the pregnant woman. Such an excretion of histidine is not characteristic of the pregnancy of the more common laboratory animals.[12] The suggested relationship between prolan and the presence of histidine in the urine[12, 13] has not been supported adequately by experimental evidence[14] and the cause of the histidinuria of human pregnancy still remains obscure. It is hoped that further studies in our laboratory may be possible in the near future.

TABLE II. THE CREATININE: HISTIDINE RATIOS IN PREGNANCY AND NONPREGNANCY URINES

	FEMALE		MALE
	PREGNANT	NONPREGNANT	
Number examined	168	59	50
Average ratio	1.14	2.35	2.73
Maximum ratio	2.64	4.43	4.84
Minimum ratio	0.45	1.08	1.34

TABLE III. HISTIDINE EXCRETION OF SUBJECT W. F. C. BEFORE, DURING, AND AFTER PREGNANCY

MONTH	CREATININE		HISTIDINE		Cr/H
	MG. PER ML.	MG. PER DAY	MG. PER ML.	MG. PER DAY	
Normal	——	——	0.215	624	——
4	0.328	1169	0.475	1690	0.69
5	0.298	972	0.343	1120	0.87
6	0.348	1369	0.364	1432	0.96
7	0.305	1147	0.347	1305	0.88
8	0.345	1002	0.549	1595	0.63
9	0.398	1166	0.490	1436	0.79
2 (Post partum)	0.325	1129	0.126	468	2.58
6 (Post partum)	0.542	——	0.198		2.74

Summary

1. The bromine method of Chattaway[11] for the determination of histidine in urine has been modified so that interference of urea is avoided and the estimation of *total* histidine is satisfactory.

2. The creatinine:histidine ratio has been determined in the urine of a large number of pregnant and nonpregnant women and of men.

3. Eighty-eight per cent of the pregnancy urines (169) examined showed low ratios, while only 9 per cent of the urines of nonpregnant women (59) and of men (50) had ratios as low as 1.70. There was no detectable difference in the ratios of nonpregnant women and men.

4. The increased excretions of urinary histidine, as evidenced by low creatinine: histidine ratios of the urine, were not found before the third month of pregnancy and cannot, therefore, be used as an aid in the early diagnosis of pregnancy.

References

1. Voge, C. I. B.: Brit. M. J. 2: 829, 1929.
2. Kapeller-Adler, R.: Biochem. Ztschr. 264: 131, 1933.
3. Kapeller-Adler, R.: Klin. Wchnschr. 15: 1728, 1936.
4. Westberg, V.: Acta obst. et gynec. Scandinav. 21: 180, 1941.
5. Page, E. W.: West, J. Surg. 51: 482, 1943.
6. Knoop, F.: Beitr. Z. chem. Physiol. u. Path. 11: 356, 1908.
7. Racker, E.: Biochem. J. 34: 89, 1940.
8. Racker, E.: Biochem. J. 35: 667, 1941.
9. Langley, W. D.: J. Biol. Chem. 137: 255, 1941.
10. Neuhardt, C. W.: Yale J. Biol. & Med. 10: 261, 1937-38.
11. Chattaway, F. W.: Biochem. J. 41: 226, 1947.
12. Kapeller-Adler, R., and Herrmann, H.: Klin. Wchnschr. 13: 1220, 1934.
13. Kapeller-Adler, R., and Herrmann, H.: Klin. Wchnschr. 15: 977, 1936.
14. Edlbacher, S., and Heitz, F.: Ztschr. f. physiol. Chem. 276: 117, 1942.

THE LEUCOCYTES DURING PREGNANCY*†

WILLIAM C. ANDREWS, M.D., AND ROY W. BONSNES, PH.D., NEW YORK, N. Y.
WITH THE TECHNICAL ASSISTANCE OF BEATRICE BARAD

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

THE leucocytes have been enumerated many times during pregnancy since Nasse in 1835 first described the white cells of the blood and also demonstrated the leucocytosis of pregnancy. References to this older literature may be found in papers by Baer[1] in 1916 and by Heyn[2] in 1924, both of whom review the literature up to that time.

Since then, there have been a few papers dealing with this subject.[3-5] However, most of the changes which occur in the circulating leucocyte picture during normal pregnancy were recognized by the time of Heyn's paper. It was known that there was an increase in the total leucocyte count and that this increase was due to an increase in the number of neutrophils. It was known that there was a further increase during labor. Heyn also described a lymphocytopenia and eosinopenia as occurring during labor. The alleged differences between the primiparous and multiparous women had not been substantiated.

Current interest in this subject has been stimulated first by the reports of White[6] and his collaborators on the reduction in the number of circulating lymphocytes observed in experimental animals and then by the reports of Forsham and Thorn and their collaborators[7, 8] on the neutrophilia, lymphopenia, and eosinopenia observed in man following the administration of either adrenal cortical extract or the adrenotrophic hormone of the anterior pituitary.

Epinephrine and insulin also produce alterations in the circulating leucocytes.[9, 10]

The alterations which occur in the circulating lymphocytes during pregnancy thus take on a new significance as possible objective indicators of changes in endocrine balance, not only during normal pregnancy, but also during some of the complications of pregnancy such as eclampsia, severe preeclampsia, and hypertensive disease. Davis and Hulit[11] have already reported the total leucocyte and eosinophil count during pregnancy. Our paper reports the results of a survey, not only of the total leucocyte count and of eosinophils, but also of the neutrophils, lymphocytes, and monocytes occurring during

*Some of these data were presented at one of the Clinical Sessions of the Joint Meeting of The Obstetrical Society of Boston, The Obstetrical Society of Philadelphia, and The New York Obstetrical Society held in New York City, April 12, 1949.

†This study was aided by a grant from the John and Mary R. Markle Foundation of New York.

pregnancy and labor, and during the complications of pregnancy, eclampsia, severe pre-eclampsia and hypertensive disease. Further, the data have been evaluated statistically.

Material

The pregnant women, both normal and those with complications, were antepartum patients at the Woman's Clinic of the New York Hospital. Those used as normal pregnant women were ambulatory patients on a routine antepartum visit to the clinic and had in most cases eaten breakfast. The blood was drawn at varying times following this meal and at varying times following their arrival at the clinic. These subjects had, therefore, been exposed to light activity followed by some rest while waiting at the clinic.

Methods

Most counts were performed on blood drawn by venipuncture with 5 ml. of blood being placed in a bottle containing mixed oxalate.[12] Blood for eosinophil counts was placed directly into a Wassermann tube containing oxalate. The tube was immersed in an ice bath before the blood was placed therein and was kept cold until the count was performed.

The total white cell count was carried out in the usual way. The differential count was done on smears made on cover slips, stained with Wright's stain. Two hundred cells were counted routinely. The eosinophils were stained and counted as described by Forsham and co-workers.[7]

Results

Total Leucocyte, Neutrophil, and Lymphocyte Counts.—

The total white count and the neutrophil and lymphocyte counts expressed as both per cent of the total white count and as absolute counts calculated from the total white counts are recorded in Table I. The *t* values for the significances between the means of these average values are given in Table II.

TABLE I. TOTAL WHITE, NEUTROPHIL, AND LYMPHOCYTE COUNTS IN PREGNANT AND NONPREGNANT WOMEN

	NUMBER	TOTAL COUNT $\times 10^3$/CU. MM.	PER CENT NEUTROPHILS	NUMBER NEUTROPHILS $\times 10^3$/CU. MM.	PER CENT LYMPHOCYTES	NUMBER LYMPHOCYTES $\times 10^3$/CU. MM.
Nonpregnant	32	7.1 ± 1.5*	63 ± 8*	4.5 ± 1.2*	29 ± 8*	2.0 ± 0.7*
Pregnant 8 to 37 weeks	75	9.2 ± 2.4	72 ± 7	6.7 ± 2.0	21 ± 6	1.9 ± 0.7
Pregnant 37 weeks +	35	10.5 ± 2.3	73 ± 6	7.7 ± 2.3	22 ± 5	2.3 ± 0.6
Labor (early)	9	12.8 ± 2.8	78 ± 5	9.8 ± 2.0	15 ± 5	1.9 ± 0.6
Labor (3-4 cm.)	7	15.7 ± 5.6	83 ± 5	13.1 ± 5.4	12 ± 5	1.6 ± 0.6
Labor (fully dilated)	10	17.4 ± 3.6	90 ± 4	15.4 ± 3.7	6 ± 4	1.1 ± 0.5
Pre-eclampsia, mild	6	10.6 ± 3.9	74 ± 6	7.9 ± 3.5	18 ± 3	1.8 ± 0.5
Pre-eclampsia, severe	16	12.6 ± 4.0	78 ± 7	10.0 ± 3.9	16 ± 6	1.9 ± 0.7
Hypertensive disease (near term)	6	9.1 ± 2.2	62 ± 8	5.7 ± 1.6	29 ± 5	2.6 ± 0.7

*Standard deviation of mean.

The relative and absolute values observed in the nonpregnant women are about the same as those cited by Wintrobe[13] for the leucocyte counts in normal adults per cubic millimeter of blood. The total and the range of the white

counts are also in good agreement with the values of 7,700 (range, 4.7 to 12.5) reported by Davis and Hulit. They are also in good agreement with the average values which have been reported under all physiological conditions.[14]

TABLE II. *t* VALUES.* VALUES IN BOLD-FACED TYPE INDICATE P LESS THAN 0.01, IN ITALICS, GREATER THAN 0.01, LESS THAN 0.05

SIGNIFICANCE OF DIFFERENCE BETWEEN	D.f.†	TOTAL COUNT	PER CENT NEUTROPHILS	NUMBER NEUTROPHILS	PER CENT LYMPHOCYTES	NUMBER LYMPHOCYTES
Pregnant and normals	105	**4.35**	**5.81**	**5.50**	**5.44**	0.69
Pregnant and severe pre-eclamptics	89	**3.30**	**9.26**	**5.44**	**2.89**	0.00
Pregnant and pregnant, late‡	108	*2.55*	0.76	*2.33*	0.85	**3.08**
Pregnant, late and labor (fully dilated)	43	**6.57**	**8.85**		**10.25**	
Pregnant, late and mild pre-eclampsia	39	0.13	0.06	0.26	**3.05**	*2.69*
Pregnant, late and severe pre-eclampsia	49	*2.56*	**3.09**	**3.03**	**4.51**	*2.35*
Pregnant, late, and hypertensive disease	39	1.21	**4.28**	*2.04*	**3.42**	1.07

*When the *t* value is in bold-faced type there is 1 chance or less in 100 that the samples considered are drawn from the same population, i.e., they are probably significantly different. When it is in italics there is more than 1 chance in 20 but less than 1 chance in 100 that the samples are drawn from the same population. When it is in ordinary type there is less than 1 chance in 20 that the samples are drawn from different populations, i.e., they are not significantly different. For further details consult Snedecor.[17]

†D.f. = Degrees of freedom.

‡Pregnant = pregnant 8 to 37 weeks. Pregnant, late = pregnant 37 weeks +.

However, all these values are above the number considered by Garrey and Bryan[14] in their review to be the average (i.e., circa 6,000) obtained after complete rest or approached after an hour of recumbent rest.

The average value for the total white count obtained by us throughout most of pregnancy is in excellent agreement with the 9,750 reported by Davis and Hulit[11] and the average value of 9,760 calculated by us from the data of Carey and Litzenberg.[3] As the statistical evaluation of our data shows, this average value is significantly different from the one obtained on nonpregnant women.

As has been known for a long time, this elevation in the white count during pregnancy is due to a neutrophilia. There is no significant change in the absolute number of lymphocytes.

As term approaches, there is a continuation of the neutrophilia and there is also a significant increase in the absolute number of lymphocytes.

Our values for the per cent of neutrophils during pregnancy is in agreement with and not significantly different from that reported by Heyn,[2] but our value for the per cent of lymphocytes is significantly lower than his average value, as calculated by us, of 24, plus or minus 3 per cent throughout pregnancy. Unfortunately, Heyn reported all his values as percentages. The total white counts are not recorded.

The data of Carey and Litzenberg[3] for the total count and the data of Heyn[2] for the percentage of neutrophils and lymphocytes show the multipara to respond to pregnancy in this respect, as does the primipara, there being no statistically significant difference between these two groups. Our data, in Table III, are in agreement, except in one instance where there is some indication that the primipara may tend to have a significantly lower percentage of lymphocytes.

The findings during labor are similar to those reported by Wolff[4] with respect to the white count. The change during labor is not only due to a neutrophilia, but also to an absolute lymphocytopenia.

TABLE III. THE TOTAL WHITE COUNT AND THE PER CENT NEUTROPHILS AND LYMPHOCYTES IN PRIMIPAROUS COMPARED TO MULTIPAROUS WOMEN

	NO.	PRIMIPAROUS	NO.	MULTIPAROUS	t*
Total White Count					
× 10³/cu. mm.—					
Pregnant†	40	9.2 ± 2.2	34	9.0 ± 2.8	0.35
Pregnant, late†	15	10.0 ± 2.6	17	11.4 ± 2.5	1.55
Neutrophils, per cent.—					
Pregnant	40	74.0 ± 5.0	34	71.0 ± 8.0	1.93
Pregnant, late	15	72.0 ± 5.0	18	74.0 ± 6.0	1.11
Lymphocytes, per cent.—					
Pregnant	40	19.0 ± 5.0	34	23.0 ± 7.0	2.85
Pregnant, late	15	23.0 ± 4.0	18	21.0 ± 5.0	1.33

*t value convention is the same as in Table II.
†Pregnant = pregnant 8 to 37 weeks. Pregnant, late = pregnant 37 weeks +.

The patients with mild pre-eclampsia have counts much like those seen in late pregnancy, though there is possibly a significant decrease in the lymphocytes as indicated.

Those with severe pre-eclampsia (including 3 with eclampsia) tend to have increased total leucocyte counts with a significantly elevated neutrophil count and a decreased lymphocyte count, which is probably significant. The percentage of lymphocytes, however, is definitely decreased in these cases because of the increase in the total count due to the neutrophilia.

Six hypertensive patients, all near term, though few in number, show an interestingly different picture and should be investigated further. A few hypertensive patients with severe pre-eclampsia superimposed on pre-existing hypertensive disease responded, as did those with severe pre-eclampsia. If these findings continue, this difference in the white count in the hypertensive patients may serve as a diagnostic aid.

Eosinophil Counts.—

Eosinophil counts have been obtained, throughout pregnancy and on normal nonpregnant women, but not on those suffering from the complications of pregnancy.

Since the variance of the average eosinophil count during normal pregnancy is so great, it is questionable if the accumulation of such data on toxemias will be of any practical value.

The eosinophil count in 21 normal women averaged 124 per cubic millimeter with a standard deviation of the mean of plus or minus 47. The count, however, seemed to be a function of the day of the cycle on which the blood was drawn, there being an indication of a downward trend in the number of eosinophils from the beginning of the cycle through the twenty-second day. In the second half of the cycle most of the counts are higher, falling off as the cycle nears completion. There are, however, only two low counts after the fifteenth day of the cycle, i.e., on the eighteenth day. If these two were cases of late ovulation, more cases might show a constant number during the first half of the cycle with a rise following ovulation. Obviously, more data must be collected. These data, however, seem to be of sufficient importance to report at this time. It is our intention to obtain additional information.

These data are not in agreement with the data of Davis and Hulit[11] who observed, in 8 women followed through the cycle, higher values for the per

cent of eosinophils in the first half of the cycle than in the second, with a marked drop at the time of ovulation (as judged by changes in basal temperature). They also report an average value of 2.3 per cent or a count of 177 eosinophils for 100 normal women.

The eosinophil count in pregnancy averaged 119 plus or minus 74 (74 patients) and during late pregnancy 113 plus or minus 107 (19 patients). These averages do not differ significantly and the variance is high. These values are again in disagreement with the values reported by Davis and Hulit,[11] who report for 200 pregnant women an average of 0.9 per cent which calculates out to be a count of 88 per cubic millimeter.

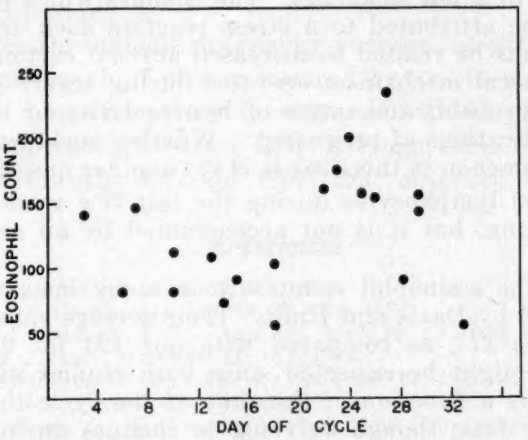


Fig. 1.—The eosinophil count per cubic millimeter as a function of the day of the menstrual cycle.

A scattergram of the data from pregnant women indicates an asymmetrical distribution of the eosinophil counts. This asymmetrical distribution is also seen in the data of Davis and Hulit for pregnant women and in the data of others. The asymmetrical distribution of the eosinophil counts in pregnancy in this sample is significant and is representative of the general population from which it was drawn.*

Monocytes.—

The per cent monocytes and the number of monocytes calculated from these values are presented in Table IV. There seems to be a decrease in the percentage of monocytes as pregnancy progresses. Though the percentage

TABLE IV. MONOCYTES

	NO.	AVERAGE	t*	
Number/cu. mm.—				
Nonpregnant	31	424 ± 165	1.49	*2.25*
Pregnant†	75	495 ± 241		
Pregnant, late†	35	550 ± 297	0.86	
Per Cent.—				
Nonpregnant	31	6.1 ± 2.2	*2.26*	2.97
Pregnant†	75	5.4 ± 2.2		
Pregnant, late†	35	4.9 ± 2.9	1.55	

*t value convention is the same as in Table II.
†Pregnant = pregnant 8 to 37 weeks. Pregnant, late = pregnant 37 weeks +.

*The index of skewness g_1 equals 1.46; the standard deviation of g_1, 0.28; and the t value for g_1, 5.2. The index of kurtosis g_2 equals 0.009.[17]

of monocytes in the late pregnant group is significantly different from the value observed in the nonpregnant group, the absolute number of monocytes is only possibly significantly different because of the increase in the total number of leucocytes. The average value obtained here for monocytes in the normal nonpregnant individual is slightly higher than that given by Wintrobe.[13] Because of the great variance observed in these data, no attempt has been made to evaluate the monocytes count during the complications of pregnancy.

Comment

To interpret these data in terms of endocrine imbalance hardly seems warranted, except in a few instances. The changes which occur during labor can undoubtedly be attributed to a stress reaction such as is expounded by Selye,[15] and can thus be related to increased adrenal cortical activity. Probably the same general mechanism operates during severe pre-eclampsia and eclampsia, and is probably indicative of hyperactivity of the adrenal cortex during these complications of pregnancy. Whether such activity is a primary or secondary phenomenon in this disease is yet another question.

The increase in lymphocytes during the last few weeks of pregnancy is an interesting finding, but it is not accompanied by an average increase in eosinophils.

Our data on the eosinophil counts are in many instances quite different from those reported by Davis and Hulit. Their average value, obtained on 100 normal women was 177, as compared with our 124 for 21 normal women. Such a difference might be expected since both studies indicate changes in eosinophil counts as a function of the time of the cycle the blood is drawn. But our respective data, though agreeing to changes during the cycle, show approximately opposite results. We observe fewer eosinophils, expressed either as counts or as per cent of the total count as the cycle progresses, with higher values during the later part of the cycle. Their data, on the other hand, show higher values during the first half of the cycle with lower values in the second half of the cycle. Their values, too, are consistently higher than ours, being about 3.75 per cent and falling to values between 3.0 to 2.0 per cent during the luteal phase of the cycle. Their data were obtained on 8 women studied throughout the cycle, while ours was obtained on 21 different women with only one blood specimen taken during one cycle.

A word of caution should be added with respect to the time of collection of blood in cases of complicated pregnancy. Obviously, counts on such patients during labor would be difficult to evaluate. Also, infusions of glucose may vitiate the values observed, since it is known that such infusions do alter the leucocyte picture (Pincus and associates[16]). However, in the normal pregnant woman (6 studied) this alteration in leucocytes has not been an invariable finding, nor has it been so in a few pre-eclamptic patients. Nevertheless, the possibility that glucose infusions might alter the leucocyte picture must be borne in mind in evaluating counts from such patients.

Summary

The findings, all evaluated statistically, with respect to the total white, neutrophil, and lymphocyte counts during normal pregnancy are in agreement with those published already, i.e., there is a leucocytosis, due mainly to a neutrophilia during pregnancy and labor with labor characterized by a more marked leucocytosis and neutrophilia, and also a lymphocytopenia. However, a significant lymphocytosis, not described previously, is observed during the last three weeks of pregnancy.

A significant increase in the number of leucocytes and neutrophils and a significant decrease in the lymphocytes are noted during severe pre-eclampsia and eclampsia but not during mild pre-eclampsia.

Eosinophil counts during pregnancy average 119 per cubic millimeter with a standard deviation of the mean of plus or minus 74 in 74 patients (one count per patient per pregnancy) throughout pregnancy, 113 plus or minus 103 in 19 patients in their last weeks of pregnancy compared to a value of 124 plus or minus 21 in 21 nonpregnant normal women. In these women the eosinophil count seems to be a function of their cycle. None of these values are significantly different.

The monocytes throughout pregnancy average 5.4 per cent with a standard deviation of the mean of plus or minus 2.2 per cent and during late pregnancy, 4.9 plus or minus 2.9 per cent, compared with 6.1 plus or minus 2.2 per cent in normal nonpregnant women. The average value observed during late pregnancy is significantly different from that observed in the nonpregnant control.

References

1. Baer, J. L.: Surg., Gynec. & Obst. **23**: 567, 1916.
2. Heyn, A.: Ztschr. f. Geburtsh. u. Gynäk. **87**: 518, 1924.
3. Carey, J. B., and Litzenberg, J. C.: Ann. Int. Med. **10**: 25, 1936.
4. Wolff, J. R.: Am. J. Obst. & Gynec. **41**: 611, 1941.
5. Cason, L. R., and Phillips, G. W.: Am. J. Clin. Path. **17**: 483, 1947.
6. White, A.: Ann. Rev. Physiol. **11**: 355, 1949.
7. Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G.: J. Clin. Endocrinol. **8**: 15, 1948.
8. Hills, A. G., Forsham, P. H., and Finch, C. A.: Blood **3**: 755, 1948.
9. Laragh, J. H., and Almy, T. P.: Proc. Soc. Exper. Biol. & Med. **69**: 499, 1949.
10. White, C., Ling, T. H., and Klein, A. M.: Blood **5**: 723, 1950.
11. Davis, M. E., and Hulit, B. E.: J. Clin. Endocrinol. **9**: 714, 1949.
12. Heller, V. G., and Paul, H.: J. Lab. & Clin. Med. **19**: 777, 1934.
13. Wintrobe, M. M.: Clinical Hematology, Philadelphia, 1942, Lea & Febiger.
14. Garrey, W. E., and Bryan, W. R.: Physiol. Rev. **15**: 597, 1935.
15. Selye, H.: Endocrinology, Acta Endocrinologica, Université de Montreal, Montreal, Canada, 1947.
16. Pincus, G., Hoagland, H., Freeman, H., Elmadjian, F., and Romanoff, L. P.: Psychosom. Med. **11**: 74, 1949.
17. Snedecor, G. W.: Statistical Methods, Iowa State College Press, Ames, Iowa, 1946.

525 East 68th Street

ACUTE APPENDICITIS INCIDENTAL TO GYNECOLOGIC ABDOMINAL PROCEDURES

E. M. Rosset, M.D., and A. S. Conston, M.D.,* Philadelphia, Pa.

(From the Department of Gynecology and the Department of Pathology, Mt. Sinai Hospital)

INCIDENTAL appendectomy is practiced in the Department of Gynecology at the Mt. Sinai Hospital, providing the nature of the primary operation permits and the appendectomy does not contribute additional hazard to the patient. All tissues excised are examined by the Department of Pathology and their report invariably comments upon the appendix. These reports have indicated a definite incidence of "acute appendicitis" as a microscopic diagnosis of the incidentally removed appendix (Table I). Since most of the patients in our Department are nonemergency admissions with a one week's wait before entering the hospital, and since they did not have obvious signs or symptoms of appendicitis, we became interested in the explanation for such findings. As a first step we re-examined our criteria for the diagnosis of appendicitis; we compared our standards for the microscopic diagnosis of early appendicitis with those of other pathologists in this area, as well as with the criteria as outlined in the various textbooks of pathology; and finally, we resurveyed the various theories of the pathogenesis of appendicitis. All this was done in the hope that we could find an explanation for the "acute appendicitis" accidentally encountered during our gynecologic abdominal procedures.

Material

In 401 abdominal gynecologic operations, from March 1, 1948, to Feb. 28, 1950, inclusive, 210 incidental appendectomies were performed. The failure to perform appendectomies in 191 cases was probably due to the unwillingness under the circumstances to expose the patient to increased risk, or because of previous appendectomy. During this period 25 cases of incidental acute appendicitis of varying degrees were diagnosed microscopically in the examination of 210 specimens (Table I). This 12 per cent incidence appeared to be strikingly high, especially since all cases with suspicious history or signs of appendicitis were discarded from the study.

The age of this group of 25 patients ranged from 22 to 46 years with 60 per cent between 35 and 45 years of age. In 21 of these 25 cases with incidental appendicitis, primary surgery was for either fibromyoma or ovarian cyst. In one case, endometriosis of the pelvic organs was the sole lesion, and in three instances it was the associated lesion. Adenomyosis was encountered twice with fibromyomas. Four major lesions of the Fallopian tubes were noted, all representing inflammatory changes of varying degrees. The operative procedure usually was total hysterectomy or removal of the affected adnexa.

*Now Chief of Laboratories, Valley Forge Army Hospital, Pa.

TABLE I. TYPE OF ACUTE APPENDICITIS NOTED IN 25 INSTANCES IN 210 INCIDENTAL APPENDECTOMIES

Acute appendicitis	7
Acute focal suppurative appendicitis	5
Low-grade acute appendicitis	6
Acute subsiding appendicitis	7
Total	25

In retrospect, we checked the clinical history of the 25 patients with "microscopic acute appendicitis." We considered a recent history of right lower quadrant abdominal pain and tenderness, elevated leucocyte count, recent fever, and nausea as the clinical criteria for diagnosis of appendicitis. In each reviewed instance where a patient had one or more of the above symptoms or signs, a pathologic lesion other than appendicitis was present to account for the symptoms (Table II). In most instances such lesions were degenerating fibromyomas or a degree of salpingitis. In one case (No. 15) early torsion of an ovarian cyst gave rise to elevated temperature, pain, and slightly increased leucocyte count.

Criteria for Histologic Diagnosis of Early Acute Appendicitis

Our histologic criteria for the earlier phases of appendicitis are based upon the presence of an appreciable number of neutrophilic leucocytes in the appendiceal lumen, or the presence of neutrophilic leucocytes in mucosal stroma, with or without luminal exudate. An increased number of eosinophiles in the tissue was taken to indicate subsidence of the acute process. We do not classify lymphoid hyperplasia, per se, as a form of appendicitis. Our criteria follow those listed by Wangensteen[11, 12] more closely than those indicated in the standard textbooks of pathology. It should be revealed that as a rule only one or two sections of an appendix are taken for study.

The majority of standard textbooks[1, 2, 3, 4] consider the earliest lesion of acute appendicitis to be a focus of acute inflammation consisting of ulceration of the epithelium with an underlying collection of neutrophiles. Herbut[5] considers the earliest evidence of an inflammatory lesion to be congestion of the mucosal and submucosal capillaries with leucocytic margination and beginning extravasation. This is similar to the description of Foot[6] and Boyd[7] for acute catarrhal appendicitis.

Five leading pathologists in the metropolitan area were questioned as to their criteria for the diagnosis of early appendicitis. The opinions varied greatly from those essentially similar to ours to those more exacting.

These basic criteria are listed as follows, each opinion being that of an individual pathologist:

1. Leucocytic extravasation in perivascular spaces.
2. The presence of leucocytes in the lumen or in the gland crypts.
3. The presence of granulocytes in the muscularis (disregarding inflammatory cells in the mucosa). When leucocytes are present in the lumen more sections are taken.
4. Leucocytic infiltration of mucosa or mucosal ulceration in addition to luminal exudate to diagnose early appendicitis.
5. Acute inflammatory cells in muscularis or serosa; or, when these cells are present in the mucosa, epithelial ulceration.

The 25 "acute" slides in our series were then re-examined and the criteria of these pathologists and those of the textbooks were applied and a composite table of diagnoses was made (Table III).

TABLE II. PATHOLOGIC LESION OTHER THAN APPENDICITIS RESPONSIBLE FOR SIGN OR SYMPTOM INDICATED

CASE NO.	RIGHT LOWER QUADRANT PAIN AND TENDERNESS	NAUSEA	PREOPERATIVE FEVER	WHITE BLOOD CELLS			APPENDIX DIAGNOSIS	LESION PROBABLY RESPONSIBLE FOR SIGN OR SYMPTOM
				NO.	SEGMENTED	NONSEGMENTED		
2	RLQ and LLQ	Yes	No	9,100	63	3	Low-grade acute	Degenerated fibromyoma
3	One episode 2 years ago	No	No	13,200	62	4	Acute	Chronic bronchiectasis with secondary polycythemia. Ovarian cyst
7	No	No	Up to 102 for 3 days	6,800	68	3	Low-grade acute	Pulmonary tuberculosis probably active, degenerated fibromyoma
8	No	No	No	14,200	76	4	Low-grade acute	Degenerating submucous myoma protruding through cervix
9	Occasionally in past 3 months	No	No	6,500	65	2	Acute focal suppurative	Endometriosis involving all pelvic organs. Perisalpingitis
15	Entire lower abdomen 3 months	No	99.4 and 99.8 once in 5 days	11,300	65	3	Acute subsiding	Benign serous cystadenoma left ovary with early torsion
17	Two months ago and recently	No	No	7,000	74	1	Acute subsiding	Right tubal pregnancy
20	Yes	No	No	8,600	60	3	Acute subsiding	Degenerated fibromyoma

By consulting Table III, one notes a downward revision from our figures of incidental appendicitis, slight in one instance and more marked in others. Nonetheless, a definite percentage exists no matter what criteria are utilized. We, therefore, can point out with assurance that the incidentally removed appendix can present inflammatory changes in a rather significant incidence.

TABLE III. VARIOUS CRITERIA AND INCIDENCE OF ACUTE APPENDICITIS ACCIDENTALLY ENCOUNTERED

CRITERIA	NO. OF CASES	% TOTAL	AGREEMENT %
Mt. Sinai Hospital series	25	12.0	
Pathology textbooks	10	4.9	40
Pathologist No. 1	22	10.5	88
Pathologist No. 2	17	8.1	68
Pathologist No. 3	8	3.8	32
Pathologist No. 4	17	8.1	68
Pathologist No. 5	17	8.1	68
Average excluding Mt. Sinai series	15.1	7.3	60

Utilizing these various groups of criteria, a definite incidence of pathologically acute appendicitis is noted to average 7.3 per cent (Table III). Shelley[8] in 2,065 consecutive incidental appendectomies noted acute appendicitis to occur in 2 per cent of his cases and chronic exudative appendicitis (late stage in recovery from acute appendicitis) in 8 per cent. This chronic exudative appendicitis is apparently similar to acute subsiding appendicitis in which the lumen, blood vessels, and perivascular tissues frequently contain some polymorphonuclear leucocytes, and there is an associated dense extensive infiltration with the various cells typical of chronic inflammation, and often chronic edema. Kline[9] in reviewing 150 consecutive incidental appendectomies found an incidence of 5 per cent acute appendicitis chiefly in association with right inguinal herniorrhaphy. In his cases there was no elevation in temperature or leucocyte count. There was nothing of significance in the history of his patients referable to acute appendicitis. The occasional case with indigestion or pain was interpreted as due to the presence of the hernia. Inspection at the operating table, he felt, was unreliable in determining absence of early appendicitis and therefore he advised routine removal and microscopic examination.

Comment

While our incidence of accidentally encountered appendicitis (12 per cent) is higher than the others quoted, we feel that a significant number of cases of asymptomatic appendicitis do occur.

The pathogenesis of appendicitis is explained by one or both of two theories. The Aschoff theory of appendicitis, supported by Gray and Haifetz, as quoted by Malloy[10] and associates, states that lymphoid hyperplasia in the appendix may cause stasis in mucosal crypts due to occlusion of either the appendiceal lumen or the crypts themselves. With stasis in crypts, inflammation within them may soon follow, spreading in the form of acute suppurative or gangrenous appendicitis.

Wangensteen and collaborators[11, 12] feel that appendicitis begins as a closed loop obstruction. They listed lymphoid hyperplasia as one of the factors which may be responsible for the obstruction. This group of workers duplicated all phases of acute appendicitis in man by ligating the bases of exteriorized appendices; a condition for success of the experiment was that the exteriorized appendix contain a secreting and relatively intact mucosa. Col-

icky pains were produced in experimental appendicitis by temporary obstruction of egress of appendiceal fluid. Early appendicular obstruction was attended by minimal inflammatory changes and release of appendiceal obstruction (early) resulted in prompt repair of the injured tissue.

Curtis,[13] in numerous gynecological operations, saw many large and comparatively healthy appendices, but was impressed with the frequency of mechanical disturbances, congenital bands and inflammatory adhesions which held the appendix in unnatural positions and might be interfering with its emptying. Anatomic peculiarities, he believed, appear to be often responsible for the development of the club-shaped appendix or other localized inflammation. Lately, Curtis has readvised routine incidental appendectomy unless there are definite contraindications.

Therefore, to explain the asymptomatic case of acute appendicitis, one must postulate the occurrence of very frequent episodes of appendicular inflammation without a predominant obstructive factor to produce symptoms. The ability of the appendix to heal has been shown by Wangensteen and his co-workers,[11, 12] and if appendicular obstruction is minimal and soon released and if the peritoneal surfaces are not involved, symptoms will not become apparent.

Many authorities[13, 14, 15] can be quoted as practicing routine incidental appendectomy, except where obviously inadvisable because of its position and difficulty in removal, or because of increased hazard to the poor-risk patient by increasing the length of the operation. Berkeley and Bonney,[16] however, dissent from this opinion.

There is no need at the present to urge the routine incidental removal of the appendix during the course of a pelvic operation, since such practice has been almost universally adopted. But it is gratifying to realize that as a result of this practice, an inflamed though asymptomatic appendix has, on occasion, been excised.

Conclusions

1. There is a definite incidence of microscopic acute appendicitis in the incidentally removed appendix.

2. Theories of pathogenesis can explain the asymptomatic case of appendicitis. If the factors of production, especially obstruction, are minimal, slight changes may occur without symptoms.

3. Acute inflammation of the appendix may occur with greater frequency than appreciated, since such episodes can be asymptomatic.

4. Continuation of routine incidental appendectomy is advisable provided risk to patient is not increased.

References

1. Boyd, William: A Text-Book of Pathology, ed. 5, Philadelphia, 1947, Lea & Febiger.
2. MacCallum, W. G.: Textbook of Pathology, ed. 6, Philadelphia, 1937, W. B. Saunders Company.
3. Ogilvie, R. F.: Pathological Histology, ed. 3, Baltimore, 1947, The Williams & Wilkins Company.
4. Forbus, Wiley D.: Reaction to Injury, Baltimore, 1943, The Williams & Wilkins Company.
5. Herbut, Peter A.: Surgical Pathology, Philadelphia, 1948, Lea & Febiger.
6. Foot, N. Chandler: Pathology in Surgery, Philadelphia, 1945, J. B. Lippincott Company.
7. Boyd, William: Surgical Pathology, ed. 6, Philadelphia, 1947, W. B. Saunders Company.
8. Shelley, H. J.: Arch. Surg. 35: 621, 1947.

9. Kline, L. B.: M. Bull. Vet. Admin. 13: 32, 1936.
10. Malloy, H. R., Jason, R. S., and Drew, C. R.: Am. J. Surg. 67: 81, 1945.
11. Wangensteen, O. H., Buirge, G. E., Dennis, C., and Ritchie, W. P.: Ann. Surg. 106: 910, 1937.
12. Burge, R. E., Dennis, C., Varco, R. L., and Wangansteen, O. H.: Arch. Path. 30: 481, 1940.
13. Curtis, Arthur H.: Textbook of Gynecology, ed. 5, Philadelphia, 1947, W. B. Saunders Company, p. 681.
14. Wharton, Lawrence R.: Gynecology With a Section on Female Urology, Philadelphia, 1943, W. B. Saunders Company, p. 733.
15. Te Linde, R. W.: Operative Gynecology, Philadelphia, 1946, J. B. Lippincott Company.
16. Berkeley, Comyns, and Bonney, Victor: A Textbook of Gynecological Surgery, ed. 5, New York, 1948, Paul B. Hoeber, Inc.

255 South 17th Street

BETA-GLUCURONIDASE STUDIES IN WOMEN

IV. The Significance of the Leucocyte Population in Vaginal Fluid*

S. C. KASDON, M.D., E. ROMSEY, A.B., F. HOMBURGER, M.D., AND
W. H. FISHMAN, PH.D., BOSTON, MASS.

(From the Cancer Research and Cancer Control Unit, Departments of Surgery, Medicine, and Biochemistry, Tufts College Medical School)

ATTENTION has been centered on the role and source of the enzyme beta-glucuronidase in physiological and pathological states. In earlier publications,[1, 2] control values for vaginal fluid and uterine cervix tissues in health and disease have been presented. It has been demonstrated that the blind vaginal pouch, with the uterus and cervix ablated, is frequently rich in beta-glucuronidase activity. Two obvious possible sources of the enzyme in vaginal fluid, *Trichomonas vaginalis* and the presence of blood elements, were considered. An evaluation has been made of the significance of the Trichomonas growing in the vaginal fluid as a contributor to the enzyme content of vaginal fluid.[3]

The present study investigates the leucocytes and their relation to vaginal fluid beta-glucuronidase activity. Since previous data on human blood and lymph[4] showed low enzyme activity in these substances, not exceeding 10 to 20 units per gram, the leucocytes,[4, 5] averaging around 1,000 units per gram, remain the most probable extraneous source rich in beta-glucuronidase.

Plan of Study

Vaginal fluid has been collected in the manner previously described[1] by means of the standard Papanicolaou pipette and bulb from 100 nonpregnant women without cancer of the genital tract. Standard smears were made as for routine exfoliative cytological study from an aliquot of the specimen used for enzyme determinations. The smears were then stained according to Papanicolaou's trichrome technique.[6] The number of leucocytes for one hundred epithelial cells from representative fields on each slide were counted in order to arrive at a reasonable estimate of the density of leucocytes in each specimen. Multiple counts on slides with large leucocyte populations showed a variation of less than 15 per cent in the total number of leucocytes per 100 epithelial cells. The number of leucocytes per 100 epithelial cells was then plotted against the beta-glucuronidase activity of the identical specimens in order to establish the relationship between the two.

*This study was aided by grants from the United States Public Health Service, the American Cancer Society, Inc., New York, and the Damon Runyon Memorial Fund for Cancer Research, New York.

Results and Comment

It can be seen from Fig. 1 that there is drift upward when the average number of leucocytes per 100 epithelial cells is plotted against the beta-glucuronidase activity in ranges of from 50 units per gram up to 400 units per gram. The scattergram of values upon which the curve was based is superimposed upon Fig. 1.

Above the last-named level, 17 observations were made in which the vaginal fluid beta-glucuronidase activity ranged regularly from 500 to 1,500 units and here the average leucocyte count per 100 epithelial cells was 394.

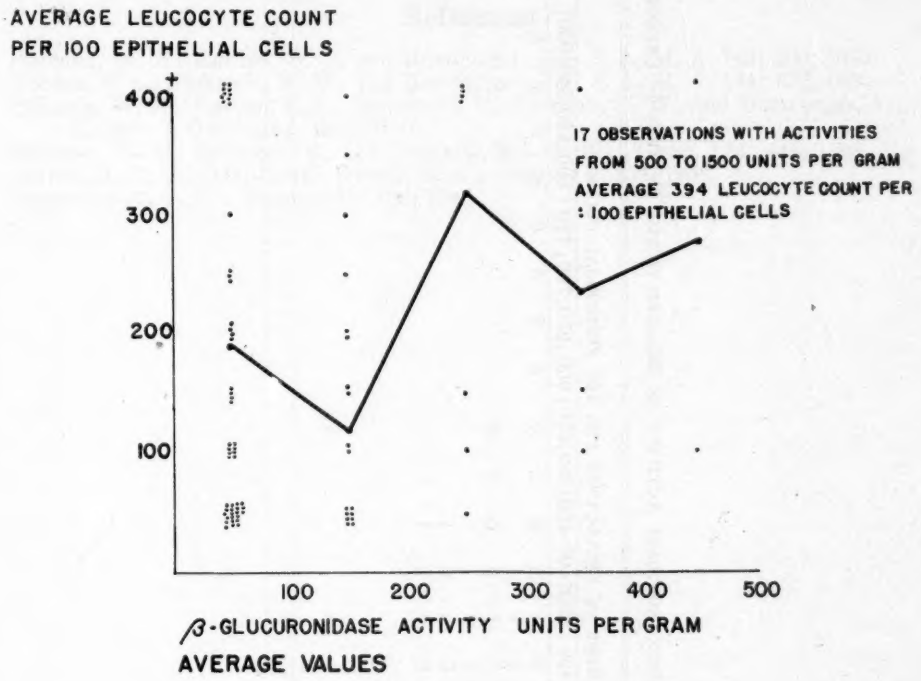


Fig. 1.

Although in the beta-glucuronidase range of 0 to 300 units per gram of vaginal fluid there is a correlation with the leucocyte population, the great number of specimens in which large numbers of leucocytes were not paralleled by high enzyme titers (sc. scattergram) makes it seem unlikely that the leucocyte population is an important source of vaginal fluid glucuronidase. Moreover, the vaginal fluids rich in beta-glucuronidase did not contain leucocytes in proportion to their activity (Table I).

The fact that so many vaginal fluids containing large numbers of leucocytes did not exhibit more than 300 units per gram of activity makes it further probable that the leucocyte population is of minor importance as a source of beta-glucuronidase in vaginal fluid.

Summary and Conclusions

Vaginal fluid specimens were collected from 100 women and were studied with respect to leucocyte population and vaginal beta-glucuronidase activity. Counts of leucocytes per 100 epithelial cells were made and related to the enzyme activity of the vaginal fluid. It was found that as the beta-glu-

TABLE I. VAGINAL FLUID BETA-GLUCURONIDASE ACTIVITY AS RELATED TO THE NUMBER OF LEUCOCYTES

BETA-GLUCURONIDASE ACTIVITY (UNITS PER GRAM)	NUMBER OF LEUCOCYTES PER 100 EPITHELIAL CELLS																					NUMBER OF COUNTS
	0	50	100	150	200	250	300	350	400	450	500	550	600	650	700	750	800	850	900	950	1,000+	
0-100	21	9	4	4	3	2	3	1	1	2	1	0	5	0	0	0	0	0	0	0	1	57
101-200	8	2	2	2	0	0	1	1	1													17
201-300	1	1	1	0	0	2	0	1	0	0	1	2										9
301-400	0	1	1	1	0	2	0	0	1													6
401-500	0	1	0	0	0	0	0	0	0	1												2
501-600	0	0	0	0	0	0	0	0	1	1												2
601-700																						
701-800	0	0	1	0	1	0	0															2
801-900																					1	1
901-1,000				1								1										2
1,001-1,500										1											1	2
Total																						100

curonidase activity rose from 0 to 300 units per gram, the leucocyte count similarly increased. However, this relationship was not linear but leveled off in the range of activity from 300 to 1,500 units per gram. There were many vaginal fluids which were rich in leucocytes and poor in beta-glucuronidase activity and conversely there were instances where a high beta-glucuronidase activity was associated with a low leucocyte count. It is concluded that the leucocyte population is of some minor importance as a source of beta-glucuronidase in the vaginal fluid.

References

1. Fishman, W. H., Kasdon, S. C., and Homburger, F.: J. A. M. A. 143: 350, 1950.
2. Kasdon, S. C., Fishman, W. H., and Homburger, F.: J. A. M. A. 144: 892, 1950.
3. Fishman, W. H., Kasdon, S. C., Bonner, C. D., Fishman, L. W., and Homburger, F.: Am. J. Obst. & Gynec. 61: 647, 1951.
4. Fishman, W. H., Springer, B., and Brunetti, R.: J. Biol. Chem. 173: 449, 1948.
5. Anlyan, A. J., Gamble, J., and Hoster, H. A.: Cancer 3: 116, 1950.
6. Papanicolaou, G. N.: Science 95: 438, 1942.

SERUM THIOCYANATE LEVELS IN PREGNANCY

D. Dalton Deeds, M.D., and Paul B. Donovan, Ph.D., San Diego, Calif.

(From the Department of Obstetrics and Gynecology of the Rees-Stealy Clinic and from the Rees-Stealy Medical Research Fund)

THE thiocyanate ion has been reported to be present in the blood serum in concentrations ranging from 0.3 mg. to 2.5 mg. (average, 1.2 mg.) per 100 c.c. of serum.[1, 2] It is thought to be derived by detoxication processes from cyanides introduced into the body in certain vegetables and, to a lesser extent, in tobacco smoke. Although relatively nontoxic, compared to the cyanides from which it is derived, the thiocyanate ion has a depressor action similar to that of the iodides and may cause death if the plasma level becomes too high.[3] It is a useful drug, however, if the plasma levels are carefully controlled[4] and many internists have used it safely and successfully, at levels ranging up to 12 mg. per cent (ten times the average normal level) for reducing the blood pressure in certain forms of hypertension. There is no doubt that the thiocyanate ion affects the blood pressure at its therapeutic levels, but there is considerable doubt as to whether or not normal blood concentrations of thiocyanate affect the blood pressure. Some authors[1] have reported that the blood pressure is inversely proportional to the blood thiocyanate level within the normal range of blood thiocyanate concentrations, and others[2, 5] have reported that there is no relation whatever between the blood pressure and normal blood concentrations of thiocyanate.

Our interest in a possible relationship between the blood pressure and the blood thiocyanate level in pregnancy was aroused by a casual observation reported by Chesley.[6] In the course of developing a new method of determining thiocyanate in biological fluids, Chesley had occasion to determine the thiocyanate content of a number of serum specimens. He reported that the thiocyanate concentrations in these specimens ranged from 0.38 mg. to 0.92 mg. (average 0.60 mg.) per 100 c.c. of serum, and remarked that these serum specimens had come from his toxemia laboratory. Since the average of these concentrations is only one-half as great as that (1.2-1.3 mg.) reported by others for presumably nonpregnant persons, we wondered whether the low thiocyanate levels observed by Chesley were related to the presence of toxemia with its accompanying hypertension, or whether such low thiocyanate levels are characteristic of normal pregnancy. We could find no reference in the literature except Chesley's to the blood thiocyanate levels in pregnancy, either in normal cases or in those complicated by toxemia. Since we considered the question sufficiently interesting to warrant further investigation, we have made simultaneous studies of blood pressure and serum thiocyanate

levels at intervals throughout a series of pregnancies and have compared the values thus obtained with the blood pressure and serum thiocyanate levels observed in a control group of nonpregnant persons.

Material

The principal subjects of this investigation were 160 private obstetrical practice patients who volunteered to undergo the slight discomfort of three or four extra venipunctures during their pregnancies. Approximately 100 of them were the brides of armed services personnel stationed in San Diego and were primigravidas in their late teens or early twenties. The remainder included a number of older women (twenty of them ranged in age from 30 to 42 years) who had had one or more previous pregnancies. There was considerable variation in serum thiocyanate level from individual to individual, but no correlation was observed between the serum thiocyanate level and either the age or the number of previous pregnancies.

The control group included 66 private practice patients who had reported to the Clinic for general physical examinations. Many of them had no symptoms of disease and none of them showed evidence of more than minimal organic lesions. This group included both sexes and ranged in age from the second through the seventh decades. The serum thiocyanate levels showed only slightly more variance than those of the pregnant group and there was no correlation between the serum thiocyanate level and either the age or sex.

No effort was made to control the diet or smoking habits of either of these groups for the purpose of this study, and blood specimens were drawn when the patient happened to be in the Clinic for some other purpose. The blood was allowed to clot and the serum was analyzed for thiocyanate by a modification of the method of Barker.[4] Since it is conceivable that the differences in serum thiocyanate concentrations reported by different investigators[1, 5, 6] were due, in part at least, to differences in methods of analysis, we have compared the results obtained by the described methods of analysis on the same pooled samples of serum. The results agreed within experimental error when the samples and the standards against which they were measured were treated in the same way. Since we used the same method for analyzing the sera of both our pregnant and nonpregnant patients, our comparison of their serum thiocyanate levels would not be invalidated even if it had been demonstrated that the apparent serum thiocyanate concentration depends on the method of analysis.

The results of our comparison of the blood pressures and serum thiocyanate levels of our pregnant patients with those of miscellaneous Clinic patients are shown in Table I. Only the systolic pressures are shown (the diastolic pressures tell the same story in a less emphatic way) and, for ease in testing whether or not the blood pressure is related to the serum thiocyanate level, these pressures have been divided into four arbitrary groups as was done by the investigators[1] who reported an inverse relationship between the (systolic) blood pressure and the serum thiocyanate level and those[2] who denied any relationship. A comparison of the average serum thiocyanate levels in the blood pressure groups indicates that the thiocyanate levels of the miscellaneous patients tend to increase with increasing blood pressure up to 140 mm. of mercury and then to fall off, whereas the thiocyanate levels of the pregnant patients tend to decrease with increasing blood pressure up to 140 and then show a slight rise. An actual calculation of correlation, however, shows that these seeming tendencies are not significant, for the correlation coefficient in both groups is less than 0.1. In this respect our results confirm the report of Connell and associates.[5]

TABLE I. RELATION OF SYSTOLIC BLOOD PRESSURE TO SERUM THIOCYANATE LEVEL OF MISCELLANEOUS AND PREGNANCY CASES

SYSTOLIC BLOOD PRESSURE (IN MM. HG)	NUMBER OF DETERMINATIONS		AV. SERUM SCN IN MG. %		DIFF.*	ERROR OF DIFF.
	MISC. PATIENTS	PREG-NANT PATIENTS	MISC. PATIENTS	PREG. PATIENTS		
Less than 100	7	39	0.80 ± 0.15	0.64 ± 0.23	0.16	±0.02
100-120	28	230	0.84 ± 0.27	0.62 ± 0.27	0.22	±0.02
120-140	25	48	0.89 ± 0.21	0.60 ± 0.17	0.29	±0.03
140 or more	6	5	0.86 ± 0.11	0.61 ± 0.24	0.25	±0.02
Av. serum SCN			0.86 ± 0.20	0.62 ± 0.21	0.24	±0.02
Av. systolic blood pressure			125 ± 28	110 ± 11	14	±1.7

*All of these differences exceed twice their error and are significant.

TABLE II. SERUM THIOCYANATE LEVELS AND BLOOD PRESSURE IN PREGNANCY BY TRIMESTERS

PERIOD	NO. OF DETERMINATIONS	SERUM SCN LEVELS				SYSTOLIC BLOOD PRESSURES		DIASTOLIC BLOOD PRESSURES	
		MEAN	STAND. DEV.	DIFF.	STAND. ERROR	MEAN AND S.D.	DIFF. AND S.E.	MEAN AND S.D.	DIFF. AND S.E.
First trimester	50	0.69	±0.18			109 ± 10		71 ± 10	
Second trimester	115	0.67	±0.25	0.02	±0.04	109 ± 12	0.0 —	69 ± 9	2.0 ±1.6
Third trimester	157	0.58	±0.18	0.09*	±0.03	111 ± 11	2.0 ±1.4	71 ± 11	2.0 ±1.3
Totals	322	0.62	±0.21	——	——	110 ± 11	— —	70 ± 10	— —
First month post partum	50	0.63	±0.18	0.05†	±0.03	112 ± 12	1.0† ±1.2	72 ± 7	1.0† ±1.1
Post partum	40	0.68	±0.23	0.10*†	±0.03	108 ± 7	3.0*† ±1.2	71 ± 7	0.0† ±0.9

*Differences greater than twice their error are significant.
†Compared with third trimester values.

The striking feature of Table I, however, is not the relationship or lack of it between serum thiocyanate and blood pressure; it is the consistent and significant differences between the thiocyanate levels of the pregnant and nonpregnant patients. In every case the serum thiocyanate level of the pregnant patients is lower than that of the nonpregnant patients by an amount that is statistically highly significant. A difference greater than twice its error is considered statistically significant and these differences exceed their errors ten or twelve times.

A further comparison of the serum thiocyanate levels and blood pressures of the pregnant patients by trimesters is shown in Table II. We do not know what the serum thiocyanate levels of these patients were before their pregnancies began, but if they were of the same order of magnitude as those of the miscellaneous patients, a fair assumption, then a drop in thiocyanate level took place very early in the first trimester, before any other evidence of hydremia. We thought that the insignificant drop shown in the second trimester was probably due to fewer cigarettes and attributed the significant drop shown in the third trimester to hydremic plethora, but we cannot account for the significant drop which must have taken place early in the first trimester. In a few instances we detected a significant drop in serum thiocyanate concentration between the first and subsequent determinations, but in most cases the results of all the determinations on any one individual were remarkably similar.

It should be noted that the serum thiocyanate levels of our patients during their normal pregnancies, and especially during the third trimester, are also remarkably similar to those of Chesley's patients with toxemia. This fact suggests that low serum thiocyanate levels are an oddity of the physiology of pregnancy and are not related to toxemia as such. We were not able to follow the serum thiocyanate levels throughout the course of toxemia since only one of these patients developed symptoms and she went to another city for her delivery. Her systolic blood pressure had risen to 150 mg. of mercury, however, and she was showing other evidences of toxemia before she left but her serum thiocyanate level showed no change whatever. The evidence seems fairly conclusive that toxemia is not related to the blood thiocyanate level.

Summary

A comparison of the serum thiocyanate levels of pregnant and nonpregnant persons indicates that the serum thiocyanate levels of pregnant persons are significantly lower than those of nonpregnant persons.

There is no correlation between the serum thiocyanate level and the blood pressure of either pregnant or nonpregnant persons.

References

1. Caviness, Verne S., Bell, Thomas A., and Satterfield, G. Howard: N. Carolina M. J. 2: 585, 1941.
2. Trasoff, Abraham, and Schneeberg, Norman G.: Am. J. M. Sc. 207: 63, 1944.
3. Kessler, Donald L., and Hines, Lawrence E.: J. A. M. A. 138: 549, 1948.
4. Barker, M. H.: J. A. M. A. 106: 762, 1936.
5. Connell, W., Ford, Wharton, G. K., and Robinson, C. E.: Am. J. M. Sc. 211: 74, 1946.
6. Chesley, Leon C.: J. Biol. Chem. 140: 135, 1941.

2001 Fourth Avenue

THE USE OF BLOOD SERUM IN THE MALE FROG TEST FOR PREGNANCY

ARTHUR L. HASKINS, M.D., AND ALFRED I. SHERMAN, M.D., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, Washington University School of Medicine)

THE gametokinetic response of the male Batrachia to gonadotrophic substances was described by Rugh in 1937.[1] The clinical application of this observation to the laboratory diagnosis of pregnancy was reported by Galli-Mainini.[2] Impetus was lent to the popularization of the male frog test for pregnancy in this country by Robbins and Parker.[3] The many published reports following in the wake of the original papers on the male frog test for pregnancy have established it as a rapid, economical, and accurate procedure in the diagnosis of pregnancy.

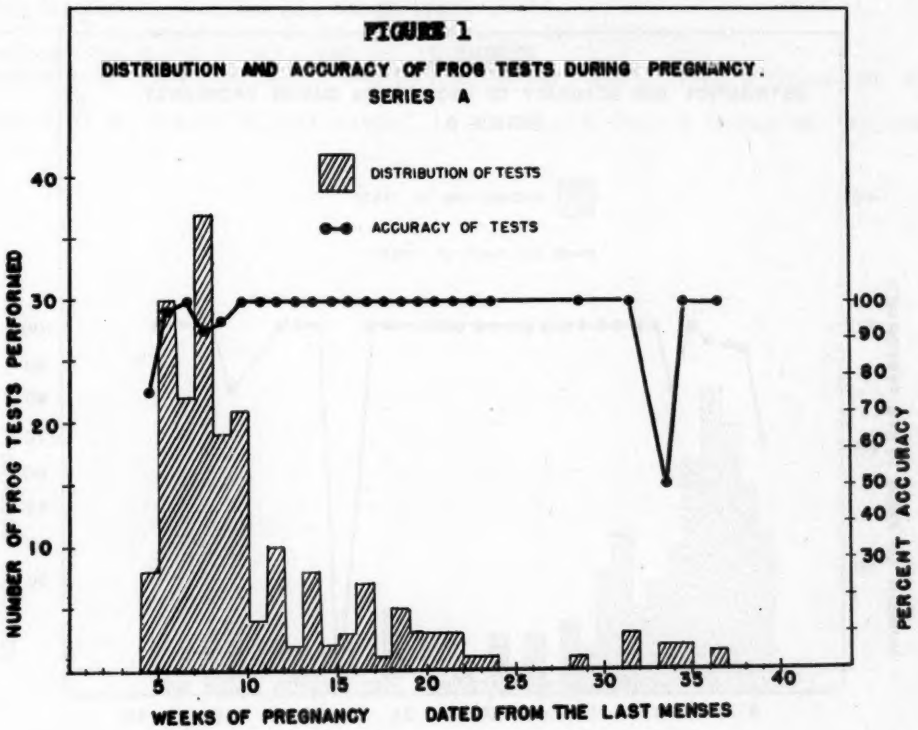
In general, pregnancy testing with the male frog has been confined almost exclusively to the use of urine as the test material. A review of the literature failed to reveal a statistically significant series of male frog tests for pregnancy in which serum was used as the testing substance. Indeed, it has been suggested[4, 5] that the use of blood serum may impair the accuracy of the procedure.

With the introduction of the male frog test for pregnancy at this institution it was soon noted that urine frequently exhibited a lethal toxicity to a significant number of test animals. Rather than subjecting the urine to detoxication procedures, blood serum was used as the test material and has been used exclusively in routine pregnancy testing. In the decision to use blood serum as the testing agent cognizance was also taken of the fact that the concentration of chorionic gonadotrophin is greater in serum than in urine.[6] The experience with male frog pregnancy testing at this institution is, therefore, considered unique since a large number of tests have been performed with serum as the testing agent. It should also be noted that the annoyance and expense of repeating tests because of premature death of the test animal has been reduced to a negligible minimum.

Procedure

Male *Rana pipiens* obtained from a single laboratory supply house were used for all pregnancy tests. Sexing of the frogs was accomplished by examination of the thenar eminences, which in the male are hypertrophied. The frogs were refrigerated at 6° C. prior to their use since this allows prolonged storage at a low metabolic level and obviates the need for feeding them. Refrigeration also reduces the incidence of stimulation of the frog to gametokinesis by amplexus.

All testing was accomplished with the use of blood serum which had been expressed by centrifugation. Contrary to the usually recommended method of injection into the dorsal or ventral lymph sac, the serum was injected intraperitoneally. This change in the injection site reduced to a minimum leakage of the serum from the needle wound. Prior to the injection of the test animal, its urine was examined for sperm. The rare test animal in which urinary sperm were found prior to injection was discarded. Three c.c. of serum were administered to each of two frogs in routine testing. After injection each frog was placed in a separate container for the remainder of the test. Urine was then obtained from the cloaca, by a small pipette, each thirty minutes until a positive response was obtained or until two hours had elapsed. A positive test was reported when urinary sperm were found in either or both frogs.



Results

From December, 1948, to March, 1950, 1,038 male frog tests were performed. Of this group it was possible to secure an adequate clinical evaluation of 800 of the patients tested. This group of 800 was divided into two groups of 400. The components of these two groups were selected at random. Each group was then treated statistically and compared to the other for the purpose of determining "predictability."

Series A included tests taken throughout the several trimesters of pregnancy but with no tests during the seventh month and only one during the tenth month of gestation. The distribution of the number of tests performed in relation to the number of weeks of gestation is depicted in Fig. 1. As would be expected from the usual experience of those doing pregnancy testing, there was a preponderance of testing performed from the fifth to the tenth week of gestation.

Of the 400 patients tested in Series A, there were 195 who proved to be pregnant. This was anticipated in 188 of the tests and the diagnosis of pregnancy was not made in 7 patients who were subsequently shown to be pregnant. Reference to Fig. 1 shows the distribution of false negative results expressed as a percentage of the total tests performed during a given week of gestation. There were 205 tests performed on nongravid patients. This group revealed 3 errors, in that the diagnosis of pregnancy was incorrectly made. This totals, of the 400, 390 correctly diagnosed; 10 incorrectly diagnosed. The accuracy was 97.5 per cent. The distribution of errors was 0.75 per cent false positive and 1.75 per cent false negative. This group also included 4 patients who were proved to have ectopic pregnancies. Of the 4, there were three positive tests and one negative. One patient with chorionepithelioma and one with a hydatidiform mole were also included among the positive tests in this series.

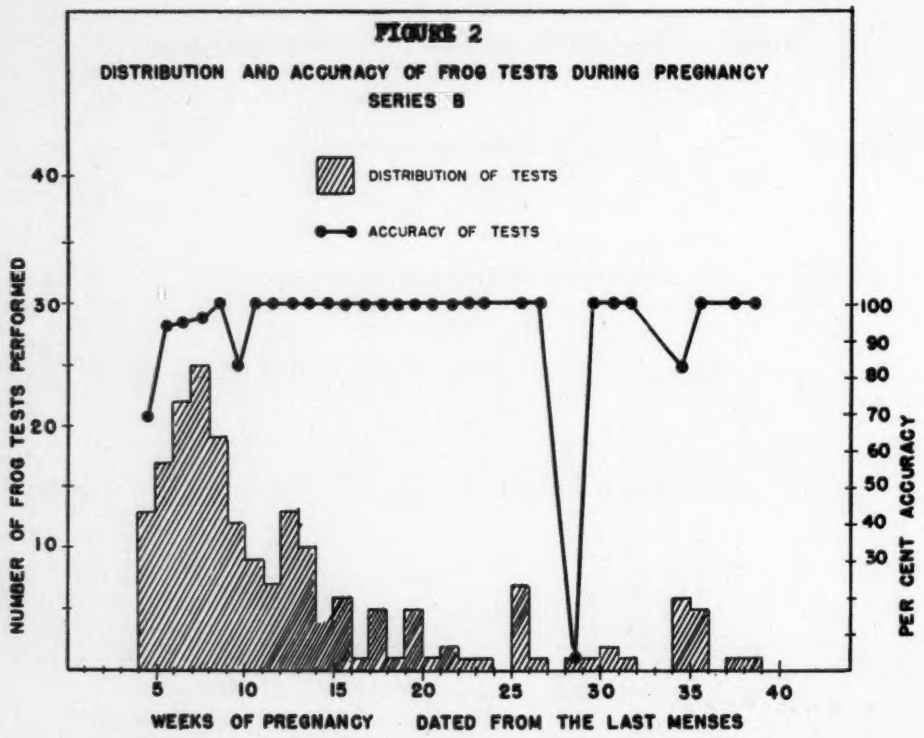


Fig. 2 illustrates the distribution of tests performed in relation to the number of weeks of gestation in the second series of 400 tests. In Series B, there was a more representative sample of tests throughout the entire duration of pregnancy. The distribution of errors did not differ fundamentally from those of Series A. Of the 400 patients tested, there were 211 found to be gravid by subsequent evaluation. Pregnancy was correctly diagnosed in 200 of these and incorrectly diagnosed in 11. In the remaining 189 nongravid patients, there were 187 negative tests and two incorrect diagnoses of pregnancy. This totals, of the 400, 387 correct diagnoses; 13 incorrect diagnoses. The accuracy was calculated as 96.75 per cent correct diagnoses. Of the incorrect diagnoses, 0.5 per cent were false positive and 2.75 per cent false negative responses. In this series there were 4 hydatidiform moles and 1 chorionepithelioma which gave rise to positive tests. Of 10 ectopic pregnancies in Series B, four produced positive and six negative responses.

Summary

A modification of the male frog test for pregnancy was described. The modification consists of the intraperitoneal injection of blood serum rather than the injection of urine into the ventral lymph sac of the frog. A review of 800 frog tests performed in this manner was presented. The accuracy of the test was 97 per cent. It was concluded that the use of serum as the testing agent in the male frog test for pregnancy does not compromise the accuracy of the test as originally described.

References

1. Rugh, R.: Proc. Soc. Exper. Biol. & Med. 36: 418, 1937.
2. Galli-Mainini, C.: Semana méd. 54: 33, 1947.
3. Robbins, S. L., and Parker, F., Jr.: Endocrinology 42: 237, 1948.
4. Galli-Mainini, C.: J. A. M. A. 138: 121, 1948.
5. Marsters, R. W., Black, M. E., and Randall, J. D.: Am. J. Obst. & Gynec. 60: 752, 1950.
6. Wilson, R. B., Albert, A., and Randall, L. M.: Am. J. Obst. & Gynec. 58: 960, 1949.

THE PSP (SPECK) TEST FOR TUBAL PATENCY

T. RICHARD HOFMANN, M.D., RICHMOND, CALIF.

(From the Gynecologic Service, Herrick Memorial Hospital, Berkeley, California, affiliated with the Department of Obstetrics and Gynecology, University of California School of Medicine)

IN 1948 Speck[1] introduced a test for determination of tubal patency by instilling phenolsulfonphthalein solution into the uterine cavity. The test is based on the contention that PSP is readily absorbed from the peritoneal cavity within 30 minutes, whereas within this period of time "... it was found that PSP is not easily absorbed (if at all) from the normal vaginal mucosa, endometrium, or endosalpinx . . . thus if the tubes are patent the PSP solution will pass from the uterus into the tubes and into the peritoneal cavity where it is absorbed, carried to the kidneys, and excreted, giving rise to a positive test. If the tubes are closed, this will not occur and the test will be negative." Speck performed the test in 24 patients and in each case the test was reported to be accurate in its determination of tubal patency. Results of the test were correlated with hysterosalpingography, transuterine insufflation, or operative findings.

Other investigators report conflicting experiences with the PSP test. Frasca[2] in Italy reports that in 15 cases he found Speck's test to be of no practical value. A positive test is possible when the tubes are closed and a negative result may be obtained when the tubes are patent.

Palán[3] in Czechoslovakia reports that in 110 cases he found the PSP test to be 100 per cent accurate. In 78 cases no control was done. In 30 cases the result was checked against hysterosalpingography and confirmed in 81.5 per cent. In 18.5 per cent (5 cases) there were intervals of several years between the hysterosalpingography and the PSP test.

Israel and Freed applied the test in 35 patients with known tubal status. Twenty of the 35 subjects had previously had bilateral cornual resection, 15 were subjects whose pelvic organs were studied by culdoscopy during the PSP test. Each of the patients with bilateral occluded tubes gave a negative Speck test. In the group studied by culdoscopy each of 10 patients with patent tubes gave a positive Speck test and each of 5 patients with obstructed tubes gave a negative Speck test. The investigators conclude "... the PSP test is a simple, economical, and safe method of recognizing tubal patency." Brown, discussing Israel and Freed's report, states, "A positive Speck test resembles shoulder pain in the insufflation test, both giving evidence of some degree of tubal patency." First presents a dissenting opinion, "... I am still not convinced of the complete accuracy of the test."

Rosset performed the PSP test upon 25 patients on the day prior to operation. In each case the condition of the pelvic organs was determined in the excised specimen. Fourteen tests (2 negative and 12 positive) were correctly correlated to the actual condition of the tubes. Five tests repre-

sented false positive reactions. (Definite color reaction in the presence of blocked tubes.) Six tests are reported as equivocal (very faint color), 3 in the presence of open tubes and 3 in the presence of closed tubes. The author concludes, "The PSP test has limited usage because of the indefinite color end points as well as the ability of some dilated, blocked, and diseased tubes to absorb the testing material (PSP solution)."

TABLE I. PATENT TUBES

PATIENT	AGE (YEARS)	GRAVIDA	C.C. DYE USED	DYE RECOVERED	HYSTERO-SALPINGOGRAM
1. E. C.	34	0	15	Yes	Tubes patent
2. I. R.	27	4	5	Yes	Tubes patent
3. L. S.	28	0	10	Yes	Tubes patent
4. R. S.	32	0	8	Yes	Tubes patent
5. R. E.	27	0	10	Yes	Tubes patent
6. M. B.	24	0	10	Yes	Tubes patent
7. J. R.	21	0	7	Yes	Tubes patent
8. P. P.	26	0	6 (2/18)	No	Tubes patent
9. L. S.	34	1	10	Yes	Tubes patent
10. C. M.	32	0	15	Yes	Tubes patent
11. D. C.	27	0	18	Yes	Tubes patent
12. C. A.	24	0	10	Yes	Tubes patent
13. E. R.	35	12	10	Yes	Tubes patent
14. M. C.	26	1	15	Yes	Tubes patent
15. B. N.	22	0	10	Yes	Tubes patent
16. M. H.	29	0	15	Yes	Tubes patent
17. L. R.	23	0	5	Yes	Tubes patent
18. J. B.	30	0	12	Yes	Tubes patent
19. E. G.	36	2	6 Yes 5 indigo carmine		
20. F. C.	30	2	15	Yes	
21. W. B.	30	0	15	Yes	
22. R. J.	33	0	20 Yes 15 indigo carmine		
23. M. D.	33	0	15	Yes	
24. O. F.	25	0	10	Yes	
25. D. S.	26	3	8	Yes	
26. V. J.	28	1	8	Yes	
27. L. S.	23	0	10	Yes	
28. M. M.	29	0	8	Yes	
29. D. B.	34	1	10	Yes	
30. R. B.	26	1	10	Yes	
31. D. J.	45	1	10	Yes	
32. M. W.	33	0	5	Yes	
33. C. H.	27	1	10	Yes	

This report reviews the writer's experience with the PSP test. Investigation began by demonstrating that PSP in solution is readily absorbed from the human peritoneal cavity. Ten c.c. PSP solution (2 ampules PSP diluted with 18 c.c. isotonic saline) were instilled into the peritoneal cavity in each of 5 patients undergoing laparotomy. Thirty minutes later catheterized urine was tested for the presence of PSP. In each case a positive result was obtained. Israel and Freed report a similar study in 15 patients. Intrauterine instillation of PSP solution was applied in 74 women with results shown in Tables I and II. Speck's technique, repeated here, was followed throughout this study excepting certain modifications mentioned later in this report.

TABLE II. OBSTRUCTED OR LIGATED TUBES

PATIENT	AGE (YEARS)	GRAVIDA	C.C. DYE USED	DYE RECOVERED	HYSTEROSALPINGOGRAM	DURATION TUBAL LIGATION
1. L. S.	36	2	8 (2/18)	No		
			10 (3/17)	Yes	Tubes closed	
2. C. N.	30	0	10	Yes	Tubes closed	
3. L. S.	29	5	5 (3/17)	No		2 years
			5 (4/16)	Yes		
4. I. F.	48	8	5	Yes		Bilateral salpingectomy 14 years
5. W. K.	43	3	6	Yes	Tubes closed	3 months
6. E. W.	30	5	8	Yes	Tubes closed	3 years
7. E. M.	25	4	15	Yes	Tubes closed	1 year
8. N. R.	39	0	5	Yes	Tubes closed	
9. S. L.	30	0	10 (2/18)	Yes	Tubes closed	
10. B. R.	35	3	5	Yes	Tubes closed	3 years
11. A. S.	27	3	12	Yes	Tubes closed	1½ years
12. G. W.	24	0	10	Yes	Tubes closed	
13. D. L.	23	3	15	Yes	Tubes closed	2 years
14. F. D.	27	4	10	Yes		2 years
			7 indigo carmine	Yes		
15. O. L.	35	4	10	Yes		1½ years
			8 indigo carmine	Yes		
16. H. B.	29	4	14	Yes		2 years
17. P. J.	33	4	8	Yes		1½ years
18. A. G.	37	2	6	Yes	Tubes closed	5 years
19. T. H.	30	2	10	Yes	Tubes closed	3 years
20. E. E.	33	3	6	Yes		3 years
21. P. C.	28	1	10	No	Tubes closed	
			6	Yes		
22. J. G.	28	4	10	Yes		1½ years
23. D. H.	27	1	5	Yes	Tubes closed	
24. D. D.	27	1	7	Yes	Tubes closed	
25. V. H.	32	0	7	Yes	Tubes closed	
26. E. B.	31	4	3	Yes		2 months
27. W. T.	27	4	3	Yes		1 year
28. S. M.	31	5	3	Yes		2 years
29. H. S.	23	1	15	Yes	Tubes closed	
30. E. M.	24	0	6	Yes	Tubes closed	
31. D. H.	30	1	8	Yes	Tubes closed	
32. W. M.	27	0	6	Yes	Tubes closed	
33. W. L.	28	2	6	Yes		Bilateral salpingectomy 3 years
34. W. W.	34	0	7	Yes	Tubes closed	
35. A. B.	27	0	8	Yes	Tubes closed	
36. J. C.	30	3	10	Yes		1½ years
37. L. H.	30	1	10	Yes	Tubes closed	
38. L. S.	38	4	10	Yes		14 years
39. J. W.	29	0	9	Yes	Tubes closed	
40. R. L.	34	4	12	Yes		2 months
41. V. O.	25	2	12	Yes		2 months

"The vagina and cervix are prepared in the same manner as for an insufflation test or hysterosalpingography. All instruments are sterile. The bladder is emptied and a Graves speculum is inserted into the vagina. The cervix is grasped with a tenaculum and the uterus probed with a uterine sound to determine depth and direction. A cannula (similar to that used with the Jarcho or Rubin apparatus) is filled with PSP solution (12 mg. or 2 c.c. of PSP solution added to 20 c.c. of isotonic saline) and inserted into the uterus, the tip being just above the internal os. The rubber obturator on the cannula fits snuggly against the external os and prevents regurgitation. A 20 c.c. syringe containing the remainder of the PSP solution is inserted into the distal end of the cannula and 10 c.c. of the solution is slowly injected into the uterine cavity. The stopcock at the distal end of the cannula is turned so that there will be no reflux of the PSP solution. The patient is given a glass of water to drink. Ten minutes are allowed to pass before the cannula is removed, for in that time the PSP solution will have passed through the tubes into the peritoneal cavity. A tampon is placed in the vagina and the patient is allowed to rest flat on the table for another twenty minutes. At the end of this time, the bladder is catheterized and the urine collected in a container. Ten per cent sodium hydroxide is added to the urine. If the urine turns pink or red, the tubes are considered patent; if there is no discoloration, closed."

Experience gained from this study suggests that the following modifications of the aforementioned technique permit more accurate evaluation of the Speck test. Instillation of a solution containing 3 ampules PSP was found to be preferred inasmuch as it produced more intense color change in alkalinized urine. This modification seemed to avoid false negative or equivocal readings. One glass of water proved insufficient for adequate diuresis. In this investigation 24 ounces of water was established as the minimum fluid intake. This quantity permits adequate excretion of the dye and tends to avoid concentrated urine in which color change is less apparent. Whereas Speck instilled 10 c.c. PSP solution in each of his patients I found that the quantity that could be instilled with ease and without patient discomfort varied from 5 to 20 c.c. In each case the urine specimen was divided into 2 portions, one sample was alkalinized with 10 per cent sodium hydroxide and compared for color change with the unalkalinized portion. Readings were made against a white background.

PSP tests were performed between days 7 and 12 following the onset of the previous menstrual period and never sooner than 2 days following the cessation of menstrual flow. Hysterosalpingography when done was performed in a greater number of cases one month after the PSP test.

Results

The PSP test was performed in 74 healthy ambulatory women. For comparison of results subjects are divided into two groups. The first group (Table I) comprises 33 women with patent tubes. The second group (Table II) 41 women with obstructed tubes. Tubal patency was confirmed by hysterosalpingography in 18 women. All other subjects in this group had normal pelvic findings, were married, and practiced contraception. In 32 of the 33 women in the group with patent tubes a positive test was obtained using a solution containing 3 ampules of PSP. In one subject (Case 8, Table I) a negative test was obtained using a solution containing 2 ampules PSP.

Indigo carmine was also used as a test solution in 4 subjects (Cases 19 and 22, Table I, Cases 14 and 15, Table II). In each subject a positive result was obtained. The technique for the indigo carmine test is the same as that employed for the PSP test. The test solution used contained two 5 c.c. (0.8 per cent) ampules indigo carmine diluted with 10 c.c. isotonic saline. A

positive test is seen as a blue-green discoloration of the unalkalized urine. No further investigation was made of the use of indigo carmine solution inasmuch as the color change in urine was difficult to detect and results seemed to parallel those of the PSP test. By use of 3 ampules of PSP in solution a negative test and a positive test were obtained in Case 21, Table II. The negative test was believed to be due to diminished urinary output.

The PSP test was performed in 41 subjects found or known to have obstructed tubes. In each case a positive test was obtained. However, in 2 cases (Nos. 1 and 3) it was necessary to increase the amount of PSP in solution to obtain a positive test. In Case 1 a negative test resulted by use of 2 ampules PSP and a positive test by use of 3 ampules PSP. In Case 3 three ampules PSP produced a negative test and 4 ampules PSP a positive test. Three ampules (18 mg.) undiluted PSP used in each of 3 cases (Nos. 26, 27, and 28) resulted in positive tests. A positive PSP and indigo carmine test was obtained in 2 cases (Nos. 14 and 15).

No complications developed in any subject in this study.

Conclusion

Contrary to the experiences of Speck, Palán, Israel and Freed, results from this investigation indicate that the PSP test is an unreliable indicator of tubal patency. The human endometrium must be considered an efficient substrate for the absorption of PSP and presumably other dyes.

References

1. Speck, G.: Am. J. Obst. & Gynec. 55: 1048, 1948.
2. Frasca, G.: Gior. di Ost. e Giu. 12: 387, 1948.
3. Palán, Fr.: Z. Por. Gyn. 88: 388, 1949.
4. Israel, S. L., and Freed, C. R.: Fertility & Sterility 1: 328, 1950.
5. Rosset, E. M.: Am. J. Obst. & Gynec. 60: 892, 1950.

803 MacDonald Avenue.

Special Article

A STUDY OF FOUR HUNDRED SEVENTY-FIVE PREGNANCIES IN AMERICAN INDIAN WOMEN

CHARLES S. MCCAMMON, M.D., FORT DEFIANCE, ARIZ.

(From the Obstetrical Service, Navaho Medical Center)

THE course of pregnancy in Indian women has received the comments of many investigators but there has been, unfortunately, no statistical evidence given to support many of the views expressed. Recently, Reid and Cohen,[1] evaluating present-day trends in obstetrics, have shown that much of the literature on this subject has been prepared by anthropologists and not by physicians engaged in obstetrical practice among Indians. Although there is no reason to discredit the anthropologists and their inquiries, it is indeed unfortunate that clinical investigators were not included in their studies.

Material

The purpose of this paper is to present a study of 475 pregnancies in American Indian women. All of the women have been cared for and studied by one physician and, with the exception of a few (less than 50 patients of the series), were delivered by the same physician. Those studied were all hospital patients and were delivered at the Navaho Medical Center between July 1, 1948, and Aug. 31, 1950. During this period there were 711 hospital deliveries; 236 of these were not under the personal observation of the author. The women were, for the most part, full-blooded Navaho Indians. A few Hopi, Zuni, and Laguna Indians are included in the study.

It is well to note that these patients were all cared for in the hospital with as good obstetrical attention as the facility and the training of the obstetrician would permit. No known study has been made of the hogan (home) deliveries attended by native midwife or medicine man. All these women came to the hospital by choice and they may possibly have had a different attitude toward pregnancy from that of the group that chose the unattended home deliveries. Furthermore, one must bear in mind that the Navaho Medical Center serves as a base hospital for five other small hospitals which refer their problems to the Center and, since certain difficult cases were evacuated to the Medical Center from field hospitals, the number of complications of pregnancy exceed those ordinarily found.

The Navaho is the largest Indian tribe of the North American continent; the Navahos live on the rugged, desert land of northern Arizona, New Mexico, and southern Utah. In this area, roughly the size of the state of West Virginia, there are few paved roads, rendering adequate transportation difficult. The Navaho Indians still live in their native hogans and live a seminomadic life. Of the estimated 67,000 Navahos, approximately 15 per cent speak English. They have retained most of their native religion and many of their customs.

At the time this study was initiated in 1948 there was neither an antepartum clinic nor a full-time obstetrician. The antepartum clinic, when initiated, was an immediate success and, at the present time, approximately 40 per cent of the women delivered in the hospital have been seen prenatally at least once. Approximately one-third of the women seen prenatally are delivered at home or in one of the smaller field hospitals.

Antepartum examinations included blood counts, serology, urinalysis, pelvimetry, complete physical examination, and, when indicated, such special procedures as roentgenograms of the pelvis, blood sugar tests, and so on.

On the obstetrical ward, the patients received supportive therapy, including vitamin K, calcium, iron, and multiple vitamin preparations. With few exceptions, all the primiparas had episiotomies at delivery, and elective outlet forceps were used. The anesthetic most often used for normal operative delivery was a saddle-block spinal with "heavy" Nupercaine. Demerol and pentobarbital sodium were used singly or in combination when sedation and analgesia seemed indicated.

It is my impression that there was much confusion among these women concerning their attitudes toward hospital deliveries. Many women frankly admitted that during the winter months they came to the hospital because it was warm and they were served acceptable food and had the use of inside toilets. Others came because they had had difficulties with previous pregnancies. Many of the younger primiparas with a little knowledge of English came because they were frightened at the prospect of labor and delivery and wanted some form of analgesia.

The members of the older group were easily frightened if a stillbirth occurred or a newborn infant expired in the hospital during their lying-in period. Not infrequently they would sign themselves out of the hospital following such an occurrence and often, following such an experience, the admissions were low for two or three weeks. I soon learned not to try to conceal fetal deaths or complications of delivery but to discuss the situation immediately with the mother in the presence of other patients. These Indians seemed to have an understanding of the dangers of syphilis, placenta previa, toxemia, prematurity, breech deliveries, and postpartum hemorrhage. They seemed to have more difficulty understanding multiple pregnancies, contracted pelvis with the resulting cesarean section, and congenital abnormalities.

It frequently seemed difficult for the older age group to understand and accept perineal shaving, enemas, dorsal lithotomy position, and the presence of a white, male physician. As an obstetrician one frequently felt guilty for laughing at the rituals of the medicine man after going through the procedure of scrubbing and preparing himself and the patient for sterile delivery.

Navaho women seemed to be intensely interested in their newborn infants and immediately after delivery attempted to see their babies, first to determine the sex and then to see if the children were normal. Fortunately, practically all of these women desired to breast feed their newborn infants and most of them had adequate milk supply for breast feeding. Navaho women seem to fondle and talk to their infants as affectionately as any mother.

Lying-in is usually a problem as many of the patients lived as far away as 200 miles from the hospital and had to travel by wagon or truck over uncertain roads to reach it. As many of the Indian women made no attempt to keep a menstrual record, or had no period between pregnancies, they frequently arrived at the hospital too early and had to wait several weeks for the onset of labor. Generally, most of them feared the surgical induction of labor and, since I am not in favor of induction without specific indications, the wards were often filled with antepartum patients.

Although most of the histories on the course of pregnancy had to be taken through an interpreter, all the patients in this series were questioned concerning miscarriage and stillbirths, nausea and vomiting, symptoms of threatened abortion and symptoms of toxemia. It should be explained that there must be some human error in the facts about to be presented, especially those based entirely upon histories. The Navaho language is considered an extremely difficult language to learn and, because of the lack of medical terminology, it is difficult to take medical histories. Also, one does not know whether his interpreter is asking leading questions to obtain an answer which the interpreter thinks is correct, or if he is interpreting clearly enough to obtain a reliable answer.

Nausea and vomiting related to pregnancy occurred in 14 per cent of this group. Although the relationship between nausea and vomiting and the ability of the women to understand and speak English was not recorded, it is my impression that at least 85 per cent of the group having nausea and vomiting spoke English. Included in this group also are some non-English speaking multiparas who had previously experienced difficult labors and deliveries. No patient has been hospitalized for nausea and vomiting and less than ten were given any form of therapy for these symptoms as outpatients.

In the same vein of thought, I have never treated a non-English speaking Indian, free of gross pelvic pathology, for dysmenorrhea, while many English speaking Indians present themselves with this complaint.

Only 30 patients of this group gave histories of previous miscarriage. During the period of this study, 57 cases of threatened, incomplete, and completed abortions were seen on the gynecology service. Sixteen of these were threatened abortions. There were 4 ectopic pregnancies. During this period there were 711 hospital deliveries. These data seem to adhere to the findings in the general population that there are fewer abortions in a rural population.[2] Although it was never proved, it is felt that criminal abortion is occasionally practiced by these Indians. During the two years of this study several women presented themselves requesting abortion, a demand which was denied.

The lay press for several years has repeatedly printed articles on the poverty and the malnutrition of the Navaho Indians. However, there has been no thorough nutritional study completed on these people. Similarly, there has been no known study made of the effects of the altitude, if any, on the hemoglobin and red blood cell values of the Navahos living at an altitude above 6,000 feet. The average hemoglobin value for 300 obstetrical patients within twenty-four hours of delivery was 11 Gm. per cent. One immediately sees that this is within normal range for the gravid patient.[2] There were 41 patients with values of less than 10 Gm. per cent. The Haden-Hausser hemoglobinometer was used in making these determinations.

For the benefit of this study, a recent survey was made of the laboratory reports of 817 individuals typed, including Rh typing. Seventy-one and three-tenths per cent of the individuals were type O, 28.3 per cent were type A, and only 0.4 per cent were type B. Of the 3 patients with type B blood, 2 were Zuni Indians, brother and sister, and one was a Navaho child. Although the Navaho child was listed as a full-blood, he presented many physical characteristics of a white child so that mixture was suspected. There were no type AB individuals. There were no Rh-negative individuals in this group.

Potter[3] suggests that approximately 100 per cent of American Indians have the Rh factor and that if an Indian without the factor is found, he should be suspected of having some white blood.

The incidence of toxemia in this group of Indian women was 13.15 per cent. Of these there were 2 with eclampsia and 23 classified as having severe

pre-eclampsia. There were no maternal deaths in this group, but there were 3 neonatal deaths. Of these infants, 2 were premature by weight, and 1 of these also had congenital syphilis (Table IV).

Of the systemic diseases complicating pregnancy, syphilis was the most prevalent with an incidence of 6.9 per cent. However, there were only two fetal deaths attributed to untreated maternal syphilis. All the patients with maternal syphilis had at least two serological tests before the diagnosis was made. Wassermann and V.D.R.L. tests were performed in all questionable cases. All live infants delivered of untreated syphilitic women were treated prophylactically regardless of the clinical findings of congenital syphilis.

A recent study[4] indicates that the incidence of syphilis among Navaho Indians for all age groups is approximately 5 per cent with an incidence of 7 to 10 per cent for the age group above 17 years of age.

The incidence of pulmonary tuberculosis is estimated to be 26 per 1,000 population among the Navahos.[5] However, only 5 cases were found in this study group. One of the group, who had negative findings in the chest x-ray at the time of delivery, was found to have an active pulmonary lesion 3 months post partum. Another patient, not included, refused hospitalization and died at home after delivering a 7-month stillborn fetus. There were 3 antepartum patients under care for active pulmonary tuberculosis at the time of the writing of this report.

There was one maternal death from tuberculosis in the series. This patient was admitted during the fourth month of pregnancy with what was felt by the medical service to be terminal pulmonary miliary tuberculosis involving all lung tissues, bilaterally. It was agreed to try to carry the patient without abortion in an attempt to save the fetus. With numerous transfusions and excellent supportive treatment, the medical service carried her to 28 weeks. A cesarean section was performed when death seemed imminent and a 2 pound, 2 ounce infant deliv ed. The infant lived 69 days, but the mother died 12 hours after surgery.

Because of the high incidence of pulmonary tuberculosis among these people, all obstetric patients have a routine roentgenogram taken of the chest before discharge.

Diabetes was not found in this study group, although diabetes does occur among Navaho Indians. There was one patient with diphtheria and there were 4 with acute pyelonephritis. One of the latter had numerous renal calculi and delivered prematurely. Only in this case did the infant fail to survive.

One patient with Sydenham's chorea was admitted at 28 weeks' gestation; this case was managed jointly by the medical and obstetrical services. The patient had a remission within 6 weeks and delivered an apparently normal baby at term.

Heart disease was found to occur with symptoms of failure in 5 individuals. One Navaho woman, admitted in acute decompensation and collapse in her thirty-sixth week of gestation, failed to respond to treatment, and died 8 hours after admission. Immediate postmortem section failed to salvage the fetus. She had not been seen prior to this admission.

Placenta previa was diagnosed in 6 patients, while a diagnosis of premature separation of the placenta was made in 3 instances.

Cesarean section was thought to be indicated in only 8 patients. The clinical diagnoses were:

1. Contraction ring, intrapartum fetal death.
2. Placenta previa, intrapartum fetal death.

3. Acute pyelonephritis with multiple renal calculi, premature infant, neonatal death.
4. Contracted pelvis, viable infant.
5. Contracted pelvis, viable infant.
6. Terminal pulmonary miliary tuberculosis, premature viable infant.
7. Placenta previa, viable infant.
8. Transverse presentation, premature labor, premature rupture of membranes, 48 hours of labor prior to admission, intrapartum fetal death.

Internal podalic version was carried out in 8 instances. Clinical diagnoses were:

1. Brow presentation, survival of baby.
2. Uterine inertia and contraction ring, survival of baby.
3. Brow-foot presentation, survival of baby.
4. Too early operative intervention with fetal distress, survival of baby.
5. Border-line pelvis with dead fetus.
6. Contraction ring, unengaged head, prolapsed cord, and fetal distress, stillbirth.
7. Brow-foot presentation with prolapsed cord, survival of baby.
8. Placenta previa centralis with dead fetus.

High forceps application and extraction were not used in any case.

In Table I are listed all the complications of pregnancy, including puerperal morbidity, found in this series. It will be noticed that the complications total 50 per cent of all deliveries, but this is high because several complications occasionally occurred in one patient. However, only 286 of the 475 patients could be listed as having a normal pregnancy, delivery, and puerperium.

TABLE I. COMPLICATIONS OF PREGNANCY, PARTURITION, AND PUERPERIUM IN FOUR HUNDRED SEVENTY-FIVE PREGNANCIES IN INDIAN WOMEN

MATERNAL COMPLICATION	NUMBER	PER CENT OF TOTAL BIRTHS
1. Toxemia	63	13.1
2. Maternal illness		
Syphilis	33	6.9
Pulmonary tuberculosis	5	1
Cardiovascular disease	5	1
Pyelonephritis	4	0.8
Diphtheria	1	
Chorea	1	
German measles	1	
Parotitis	1	
Thyrotoxicosis	1	
3. Bleeding		
Placenta previa	6	1.3
Abruptio placentae	3	0.6
4. Abnormal presentation (including breech)	27	5.7
5. Contracted pelvis	3	0.6
6. Contraction ring	4	0.8
7. Premature delivery	34	7.1
8. Multiple pregnancies	8	1.7
9. Postpartum hemorrhage	8	1.7
10. Postpartum pneumonia	2	
11. Postpartum phlebothrombosis	2	
12. Puerperal morbidity	33	6.9
Total	245	50.1

Many confusing impressions have been given concerning the labor and delivery of Indian women. DeLee[2] states, "The length of parturition is variable, which is true also of the same women in different labors. In the uncivilized races labor is much shorter. It is said that some Indian women, while the tribe is on the march, feeling the pains of labor coming on, go off to the side of the underbrush, bear the child, and, after expressing the afterbirth, hurry to catch up with the rest of the train, but this is exceptional and true only of pure breeds." In the Southeastern mountains where I lived as a child, it was not unusual to hear physicians speak of white women who delivered unattended and immediately went about their household tasks. One of the nurses on our obstetrical service who spent several years with the Frontier Nursing Service in the mountains of Kentucky stated that nurses frequently have difficulty in delaying the mother's return to the household duties for even two days after the birth of a baby.

Of this group of Indian women, it was possible to obtain a satisfactory length of labor in the cases of 52 primiparas and 156 multiparas. Length of labor in this group was from the time the patient stated that she recognized labor until the birth of the baby. (Delivery of placenta was not delayed more than 15 minutes in any of these cases.) The average length of labor in the primiparas was 18 hours and 40 minutes, while in the multiparas, it was 11 hours and 10 minutes. The usually accepted length of labor for white women is 18 and 12 hours, respectively.[2] Therefore, the length of labor for Indians is essentially the same as in the general population. It should be pointed out that elective outlet forceps and episiotomies were used in the delivery of most of these primiparas, thus appreciably shortening the second stage. In the recording of the length of labor, false labor was not recorded, although it undoubtedly helps to start cervical effacement.

The average age for the 100 primiparas of this series was 20.5 years. There were 6 women 16 years of age or younger, the youngest being 13 years old. There were 4 women 30 years of age or older, with the oldest age for a first pregnancy being 32 years. Of the 208 women in whom length of labor was recorded, 36 had labors over 20 hours. One would expect a high incidence of prolonged labor in a population such as the Navahos because of the many grand multiparas. Of these 475 women, 33 were 40 years of age or older, and 75 had had 8 or more pregnancies.

For anyone to say that Indian women do not experience pain during labor is to admit that he had never attended an Indian during labor. Many appear to suffer severe pain for many hours; these women do not hesitate to request analgesics and anesthetics. Others said that they came to the hospital only because they wanted something to relieve their pain. However, I am convinced that not a few go through labor and delivery without pain.

Investigating the Navaho language, one finds that there are specific words for both labor and pain of labor. There are no words compatible with "morning sickness" or dysmenorrhea.

Some form of anesthesia was felt necessary in 27.3 per cent of the deliveries. Local anesthetic alone and not in combination with an inhalation anesthetic was used in 13 per cent of the 130 deliveries in which an anesthetic was used.

There seemed to be two distinct groups of Indian women—one group had no fear of labor; they took it as a matter of course. The other group feared labor and needed assistance in the form of analgesia and anesthesia. Practically all of the first group were non-English speaking Indians who had had little contact with the white man and his ways.

The statement quoted from Dr. DeLee concerning Indians in labor keeps returning to mind, especially the ending, "but this is exceptional and true

only of pure breeds." May it not be true that a pure breed is better adapted anatomically and physiologically to bear children than women of mixed blood? Add to this the psychological adaptability caused by the simple, natural way of life, unhampered by the mental tension and driving urge to be "highly civilized," and one may explain the ease with which many of the Navaho women bear children.

Believing in the desirability of early ambulation, I insisted on this practice until I became interested in the Navaho idea of pregnancy and parturition and decided to let each woman do as she desired about ambulation. The primiparas and young multiparas were practically always up after a few hours' rest. The group of grand multiparas tended to spend several hours a day resting and were up only for bathroom privileges and for personal care. Catheterization of a postpartum Navaho patient is rarely necessary following complete recovery from anesthesia.

One is astounded at the apparent cleanliness of the vagina in Navaho women who know nothing of douches and personal hygiene, as we use the term. Few Navaho women wear undergarments and the great majority apparently do not use perineal pads during menstruation. This may have some relationship to the fact that only 8 cases of uterine carcinoma have been diagnosed among 6,685 hospital admissions during the period of this study.

Table II shows the breakdown as to presentation as well as multiple pregnancy. Table III shows the breakdown of 377 vertex presentations.

TABLE II. PRESENTATION IN FOUR HUNDRED SEVENTY-FIVE PREGNANCIES

PRESENTATION	NUMBER	PERCENTAGE OF TOTAL BIRTHS
Vertex	450 (not including multiple pregnancies)	94.7
Breech	11 (not including multiple pregnancies)	2.3
Twins	8	1.7
Brow	4	0.8
Transverse	2	0.5
Total	475	100.0

TABLE III. POSITION IN THREE HUNDRED SEVENTY-SEVEN VERTEX PRESENTATIONS

VERTEX	NUMBER	PER CENT
Left occipitoanterior-left occipitotransverse	183	48.5
Right occipitoanterior-right occipitotransverse	104	27.6
Left occipitoposterior	51	13.5
Right occipitoposterior	39	10.4
Total	377	100.0

The average birth weight for 528 infants delivered at this facility since Jan. 1, 1949, was 7 pounds. There were only 9 babies weighing 9 pounds and over, the largest weighing 10 pounds, 4 ounces. However, there were 34 babies weighing 5 pounds, 8 ounces or less, with the smallest to survive the first month of life weighing 2 pounds, 2 ounces. Of these 34 premature babies, 9 were from multiple pregnancies. Four premature babies failed to survive the neonatal period, and 4 were stillborn. Table IV shows the stillbirths and neonatal deaths in relation to clinical diagnosis.

Congenital anomalies occurred in 8 infants. There was 1 case of hydrocephalus, 1 infant with congenital ichthyosis, 1 with webbed toes, 1 with

webbed fingers, 2 with polydactylism, and 2 cases microtia. Two infants were born with hemangiomas.

The puerperal morbidity (temperature of 100° F. or higher for at least 2 days in succession) for this group was 6.19 per cent. There were 2 maternal deaths, both of which seemed unpreventable at the stage when they were first seen.

TABLE IV. STILLBIRTHS AND NEONATAL DEATHS IN FOUR HUNDRED EIGHTY-THREE BIRTHS

CLINICAL DIAGNOSIS	NUMBER
Dead on Admission.—	
Placenta previa	1
Abruptio placentae	1
Syphilis	1
Congenital anomalies	2
Cause unknown	2
Total	7
Died During Labor.—	
Breech with prolapsed cord	2
Transverse, prematurity	1
Contraction ring	2
Congenital anomaly, placenta previa, prematurity	1
Placenta previa	1
Cause unknown	2
Total	9
Neonatal Deaths.—	
Syphilis, prematurity, and toxemia	1
Prematurity	2
Toxemia	1
Toxemia and prematurity	2
Pneumonia, newborn infant	1
Cause unknown	1
Total	8
Complete total	24

Summary

A study of 475 pregnancies in Indian women, mostly full-blooded Navaho Indians, is presented, with special emphasis on the duration of labor and the presence of painful labor.

Conclusions

1. Indian women experience all the complications and unpleasant symptoms of pregnancy and labor experienced by non-Indian women.

2. The incidence of nausea and vomiting of pregnancy, abortion, and threatened abortion seems remarkably lower than in non-Indians.

3. Although many Indian women experience severe pain during labor, many others apparently experience little or no pain.

4. The duration of labor in Indians is essentially the same as for non-Indians.

References

1. Reid, D. E., and Cohen, M. E.: J. A. M. A. 142: 615, 1950.
2. DeLee, Joseph B., and Greenhill, J. P.: The Principles and Practice of Obstetrics, Ed. 8, Philadelphia, 1943, W. B. Saunders Company.
3. Potter, E. L.: Rh—Its Relation to Congenital Hemolytic Diseases to Intragroup Transfusion Reactions, Year Book Pub., 1947.
4. McCammon, C. S., et al.: J. Ven. Dis. Inform. 32: 28, 1951.
5. Statistical Section, Health Branch, Navaho Indian Agency Bureau of Indian Affairs, 1949, 1951.

Department of Case Reports New Instruments, Etc.

DYSGERMINOMA OF THE OVARY WITH ASSOCIATED TUBERCULOID REACTION IN LUNGS AND LYMPH NODES

LEWIS R. WEINTRAUB, M.D., PHILIP ROSENBLATT, M.D., AND LEONARD BRANDMAN, M.D., BROOKLYN, N. Y.

(From the Department of Laboratories, Jewish Hospital of Brooklyn)

THE incidence of an associated tuberculoid reaction with this tumor is an extremely rare occurrence. To date only two cases have been reported.[1] In each of these cases the tuberculoid reaction was found in the Fallopian tube and was initially mistaken for tuberculous salpingitis. In addition to these two cases, Heller cites four other cases in which there was demonstrated a tuberculoid reaction within the tumor itself. Our case is the first in which this reaction is reported at foci distant from the tumor iself. These occurred in the lungs and lymph nodes in widely scattered areas.

The patient was a 78-year-old white woman admitted to the Jewish Hospital of Brooklyn on Nov. 3, 1948. She had no complaints except for constipation of many years' duration which had become more severe during the past few months. One month prior to admission she developed severe pain in the lower abdomen and back which was of varying intensity. There was associated nausea and anorexia. She also complained of slight dysuria during the past few weeks. Menstruation began at the age of 13, occurred regularly every 28 days and lasted 4 days. Except for slight dysmenorrhea her menstrual history had not been unusual. The menopause took place at the age of 50. She had been married but never pregnant.

Physical Examination.—The patient was poorly nourished. The temperature was 98.8° F., pulse 78, and blood pressure 116/65. The chest was clear. The heart was somewhat enlarged to the left with occasional irregularities of rhythm. The abdomen was distended but no organs were palpable. Pelvic examination revealed a firm, undefined mass extending beyond the vault. Rectal examination revealed a firm, irregular, fixed, nontender mass, which appeared to be in the pelvis fixed to the anterior rectal wall.

Laboratory Data.—Hemoglobin was 98 per cent, red cells 5,060,000 per cubic millimeter, white cells 6,850 per cubic millimeter with 56 per cent polymorphonuclear leucocytes and 44 per cent lymphocytes. Urine analysis was negative. The sedimentation rate was 11 mm. in 60 minutes (Westergren). The blood sugar, urea, phosphatase, and protein were normal. The cephalin flocculation was 2+. The thymol turbidity was 7 units. The Wassermann test for syphilis was negative. The prothrombin time was normal.

Roentgen studies of the chest, skull, and intestine were all within normal limits.

Course in Hospital.—Eight days after admission an exploratory laparotomy was performed. An extensive inoperable tumor was found in the pelvis, fixing and obliterating all the viscera. Following operation the patient did poorly. Abdominal pain and distention developed. Ascites was noted and one month postoperatively the patient died.

Autosy Findings.—Weight was 48 kg. There were 700 c.c. of clear yellow fluid in each pleural cavity and fibrinous adhesions between the lungs and chest walls. There were several firm nodular implants measuring up to 0.5 cm. in diameter on the pericardium and

the pericardial cavity contained 75 c.c. of clear pink fluid. The peritoneal cavity contained 1,200 c.c. of pink-stained fluid. The peritoneum was studded with small gray-white nodules measuring up to 1.5 cm. in diameter. In the lower abdomen and pelvis was a large, firm, rubbery pink gray white mass. In it were fixed the cecum and a portion of transverse colon as well as the uterus and both adnexal regions. The Fallopian tubes could be dissected out with difficulty. The mass was irregular in outline and measured approximately 20 cm. in diameter. There were several areas of softening and a few cysts were noted. There were numerous adhesions within the peritoneal cavity. Several enlarged tracheobronchial and para-aortic nodes were present. The heart weighed 200 grams and showed a moderate degree of fatty infiltration and myocardial fibrosis. The lungs showed congestion and atelectasis and contained several small firm nodules measuring up to 0.7 cm. The liver weighed 2,000 grams and was studded with numerous implants of tumor tissue. The spleen was congested and there were tumor implants in the capsule. The adrenal glands and kidneys were not remarkable. The uterus was completely surrounded, fixed, and partly invaded by tumor tissue. The ovaries were poorly defined and almost completely replaced by tumor.

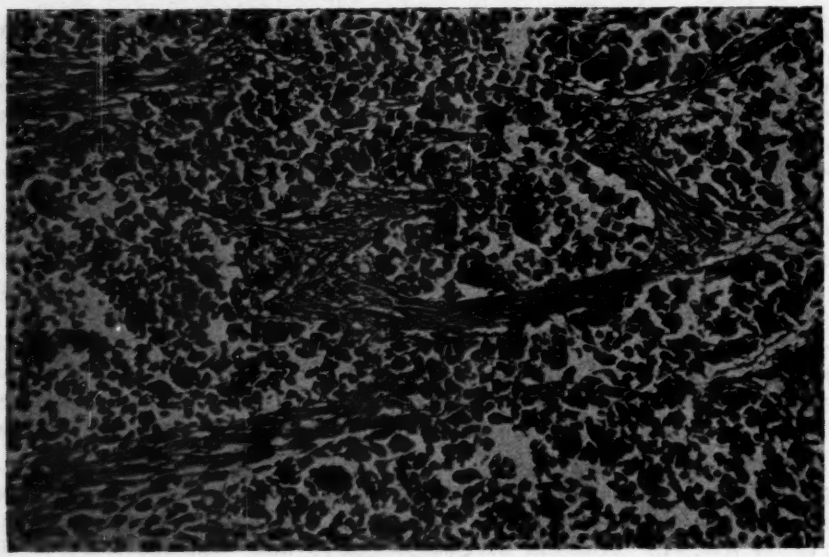


Fig. 1.—Dysgerminoma of ovary.

Microscopic Examination.—Ovarian region: No normal ovarian tissue could be recognized. Instead there was tumor which was composed of large round, oval, and polygonal cells with homogeneous pink-staining cytoplasm. The nuclei were large, deeply staining, and vesicular with a well-defined border. The cells themselves varied in size and occasional giant cells were seen. Mitotic figures were present in some places. The cells were arranged in cords which were separated by broad and narrow bands of loose pale pink-staining connective tissue. The tumor cells lay free within the spaces formed by these septa. Areas of necrosis were also present.

Lungs: There were scattered areas of atelectasis and emphysema. In one place was a large irregular area of fibrosis. The ground substance was hyalinized in most places. Scattered throughout in regular fashion were collections of lymphocytes and peculiar giant cells of varying configuration. In places the giant and lymphoid cells formed focal accumulations resembling granulomatous formation. The giant cells were irregular in shape, large, and multinucleated. The nuclei varied in number from three to twenty. In some cells they were peripherally distributed. In others nuclei were centrally disposed or were

irregularly scattered throughout the cytoplasm. The nuclei tended to be oval in shape, had a coarse chromatin network, and no nucleoli were seen. The cytoplasm was pink staining and variable in consistency. In some cells it appeared granular and homogeneous. In others the cytoplasm contained irregular clear spaces which resembled vacuoles and which gave the cells a somewhat moth-eaten appearance. In places accumulations of giant cells and lymphoid cells were seen to extend into contiguous thickened septa. Distended capillaries were scattered throughout.

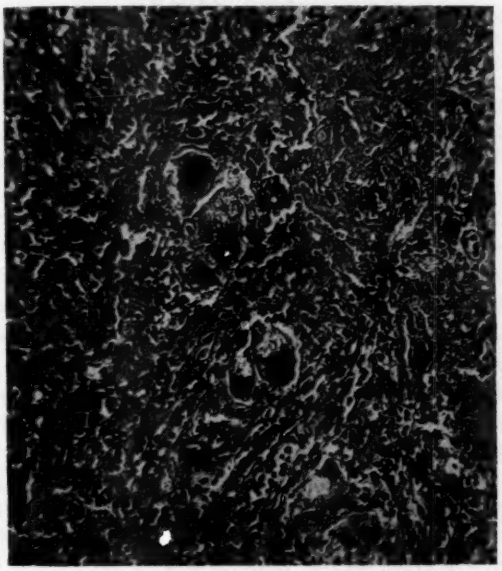


Fig. 2.—Granulomatous lesion in lung with peculiar giant cells.

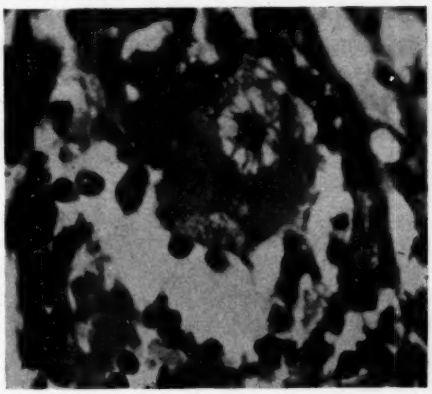


Fig. 3.—Giant cell in lymph node showing asteroid body.

Para-aortic Lymph Node: The usual architecture was well maintained but somewhat exaggerated. Follicles were large and in places there was a marked increase in the number of reticulum cells. Within some of the follicles were deposits of homogeneous hyaline material resembling para-amyloid. The lymphoid sinuses were crowded with large mononuclear cells and in one place there was a nest of tumor similar to that found in the ovarian region. Within the pulp there was a somewhat diffuse collection of lymphocytes, plasma cells, and small mononuclear cells. Here, too, there were giant cells of the type described above. In addition one giant cell was seen which had a single large rounded nucleus with

clear nucleoplasm. The nuclear membrane was represented by a thin line which separated it from the coarsely granular cytoplasm. In the center of the nucleus was an irregularly rounded condensation of chromatin from which radiating lines extended in radial fashion to end at the nuclear membrane, giving a star sapphire appearance.

Preparation from another para-aortic node showed an entirely different picture. Here normal architecture was seen only at the periphery of the node. The remainder was largely replaced by broad bands of hyalinized fibrous connective tissue. Scattered throughout were multinucleated giant cells of the types described above, as well as diffuse collections of round cells. Small foci of necrosis were also seen but no tumor could be recognized.

Tracheobronchial Lymph Node: Sections from the tracheobronchial lymph node revealed a picture intermediate between the above-described nodes. In places there were focal collections of giant cells and lymphoid cells which made up a definite granulomatous pattern. Other lymph nodes contained tumor deposits in association with the above-described lesions.

Sections of the lymph nodes stained with scarlet R revealed a moderate amount of lipoid material both within the cytoplasm of the giant cells and within the parenchyma of the nodes.

Microscopic preparations of other organs revealed no unusual features other than tumor metastases and congestion.

Anatomic Diagnosis: Dysgerminoma of ovaries with metastases in uterus, Fallopian tubes, peritoneum, liver, spleen, pancreas, gall bladder, and intestines; bilateral hydrothorax; ascites; arteriosclerosis of aorta, cerebral, and coronary arteries; myofibrosis cordis; atelectasis and emphysema of lungs; tubercle-like formations in lung and lymph nodes.

Comment: The case reported here is unique from two points of view. Inasmuch as the majority of cases occur in girls shortly after the onset of puberty, the finding of a dysgerminoma in a woman of 78 is extremely unusual. A careful search of the literature reveals this to be the oldest patient in whom an ovarian dysgerminoma was found. The oldest previously reported patient was 52 years of age.

The finding of a tuberculoid reaction in the lungs and lymph nodes is unusual in that there are no other cases reported in which this reaction occurred in organs distant from the ovary.

The exact nature of these lesions has not been definitely established. However, the finding of abundant lipoid material in the giant cells in areas distant from the tumor itself lends support to the theory that a lipoid substance is elaborated by the tumor and is capable of stimulating a tuberculoid reaction in distant susceptible organs.

Reference

1. Heller, E. L.: Arch. Path. 35: 674, 1943.

555 Prospect Place.

NORMAL SALINE INSTILLATION AS A TEST FOR TUBAL PATENCY

Preliminary Report

MANUEL C. LORES, M.D., MIAMI, FLA.

TWO procedures commonly used in testing the patency of the Fallopian tubes are tubal insufflation and hysterosalpingography.

In the former, carbon dioxide or air is insufflated through the cervical os. Its escape into the abdominal cavity is verified by suprapubic auscultation, the fall in the manometric pressure, the production of shoulder pain when the patient assumes the erect posture, or the radiologic demonstration of a gas meniscus under the diaphragm. Meigs and Sturgis[1] stress the fact that unless the patient has unmistakable shoulder pain on resuming the erect position after the test, such test must be considered a failure and must be repeated, even though a drop in the manometric pressure and suprapubic auscultation suggest the passage of the gas. Crossen[2] advises that in doubtful cases an x-ray be taken to demonstrate the presence of a subphrenic pneumoperitoneum. These absolute evidences of the presence of the insufflated gas in the abdominal cavity are essential because of the difficulties of detecting the leakage of gas, especially at the junction of the cannula with the external os.

Hysterosalpingography may be done after tubal insufflation has indicated obstruction in the tubes.[3] In hysterosalpingography a radiopaque substance is injected into the uterine cavity. The filling of the uterus and tubes and the progress of the substance may be observed under the fluoroscope. X-ray films are made during and subsequent to the procedure for record and further study. As Feiner[3] has stated, such injection of a radiopaque substance is not an inocuous procedure and as a diagnostic method these injections carry a certain morbidity and mortality, although small.[4] When Lipiodol is used a foreign substance of slow or minimal assimilation is introduced into the tubes, the pelvic and abdominal cavities. Rubin[5] has demonstrated radiopaque deposits at one month to a year and longer in the tubes, the pelvis, and upper abdominal cavity and also the production of Lipiodol granulomas in the Fallopian tubes. The accidental injection of ovarian and pelvic veins with the production of anaphylactoid reactions and the presence of pulmonary embolism have been reported also.[4, 6, 7]

To avoid such hazards and uncertainties, the author reports his use of sterile normal saline to demonstrate tubal patency.

Procedure.—The test is performed in the preovulation period. The cervix is exposed with a Graves speculum. It is cleaned and swabbed with an antiseptic solution. Using a Jarcho pressometer (or any other similar instrument) and a standard insufflation cannula, 20 to 30 c.c. of sterile normal saline are injected under manometric pressure. Since the injected medium is a liquid, any leak in the circuit is easily detected. If after the instillation the vagina is dry and no visible leakage has occurred at any instrumental connection, it is obvious that any utilized number of cubic centimeters of the normal saline must have progressed upward. Constant observation of the manometer is made in the usual manner and for the usual records and inferences, as in the routine insufflation of gas.

The use of a physiologic solution, sterile normal saline, to determine tubal patency has certain advantages over gas and/or radiopaque substances:

1. Leaks in the circuit are easily detected and corrected. This is sometimes difficult when gas is insufflated, as evidenced by the rigid criteria set as proof of the presence of the gas in the abdominal cavity.[1, 2]

2. Reactions due to idiosyncrasy, such as occur at times with radiopaque materials, are eliminated.[4]

3. There is complete freedom from the dangers of embolic phenomena.[4, 6, 7]

4. Because of the nonirritating nature and absorbability of the normal saline there is no danger of reactions in the tubes and pelvic cavity.[7]

5. The freedom from any abdominal discomfort and/or shoulder pain permits the patient to get up from the examining table immediately after the instillation and walk home.

6. No x-ray facilities or complicated apparatus are required.

7. The test can be repeated as often as necessary, both for diagnostic and therapeutic indications, because of the complete lack of discomfort to the patient.

I want to acknowledge my appreciation to Dr. Robert T. Spicer and Dr. Carlos P. Lamar for their help and invaluable advice.

References

1. Meigs, J. V., and Sturgis, S. H.: Progress in Gynecology, New York, 1946, Grune and Stratton, Inc., p. 249.
2. Crossen, H. S., and Crossen, R. J.: Diseases of Women, St. Louis, 1935, The C. V. Mosby Company, p. 330.
3. Feiner, David: AM. J. OBST. & GYNEC. 43: 639, 1942.
4. Schaffer, B.: Boll. Soc. de obst. y ginec. de Buenos Aires 20: 517, 1941.
5. Rubin, I. C.: Radiology 33: 350, 1939.
6. Campos da Paz, A.: Rev. de ginec. e d'obst. 1: 244, 1945.
7. Eisen, D., and Goldstein, J.: Radiology 45: 603, 1945.

FETAL EXSANGUINATION AND ITS SUCCESSFUL TREATMENT

LIEUTENANT (JG) JONATHAN G. BUSBY, MC, USN, AND LIEUTENANT (JG) ROBERT F. NEAL, MC, USN

(From the Department of Obstetrics and Gynecology, and the Department of Pediatrics, United States Naval Hospital, Bethesda, Md.)

IN THIS case traction produced on a short umbilical cord during the second stage of labor apparently caused the rupture of a small communicating vein in the marginal insertion of the umbilical cord, resulting in exsanguination of the infant. The infant survived due to the immediate catheterization of and transfusion into the umbilical vein. The case is reported to emphasize the necessity of immediate transfusion of the infant.

F. F., a 19-year-old white primigravida with an expected date of confinement of May 1, 1950, was admitted to the hospital in active labor at 3 A.M., on May 1, 1950.

The patient's prenatal course had been uneventful until April 22, 1950, at which time she had been hospitalized because of overweight and moderate edema of the hands. At this time she had gained twenty-five pounds; the blood pressure was 130/100; the serologic examination was negative; the Rh factor was positive; the urinalysis was negative; and the hemoglobin was 12.5 Gm. per cent. The patient was placed on a liquid reduction diet, magnesium sulfate orally, and complete bed rest for six days. While on bed rest, the patient was thought to have ruptured the membranes, although the leakage was minimal. Therefore, she was placed on sulfadiazine and penicillin until the membranes apparently sealed spontaneously two days later. At the end of this period, the symptoms of mild toxemia had disappeared, the blood pressure was normal, the patient had lost seven pounds, and she was discharged to await the onset of labor.

Upon readmission, she had an uneventful progressive labor, and was sedated with Seconal, 3 grains, Demerol, 100 mg., and scopolamine, 1/150 grain, at 10:30 A.M. and 11:15 A.M. respectively. The patient was taken to the delivery room at 12 noon with the perineum bulging. The fetal heartbeat was 140 and regular at this time. The bulging membranes were ruptured artifically, and the fetal heart remained stable at 140.

A few minutes later, while a pudendal block was being given, the patient had a strong contraction followed by a gush of 50 to 100 c.c. of bright red blood from the vagina. With the thought that perhaps a terminal placental separation was taking place, low forceps were applied immediately, and a 6-pound male child was delivered over a left mediolateral episiotomy at 12:10 P.M.

The placenta separated spontaneously and was expressed intact five minutes later. The umbilical cord was found to be 26 cm. in length, and had been tightly wrapped once around the baby's neck. There was a marginal insertion of the umbilical cord into a battledore placenta with the rupture of a small vein which communicated with the central vein of the cord.

The child appeared to be suffering from asphyxia pallida, and the cord was not pulsating. Shallow respirations began spontaneously, but the child did not cry, nor did his color improve under continuous oxygen inhalations.

The pediatrician, who was summoned immediately, could elicit no history of Rh incompatibility or other blood dyscrasia. There was no icterus of the skin, cord, or amniotic fluid. Regardless of the cause, it was assumed that the baby was suffering from an extreme degree of anemia, and was in shock.

Because of the infant's desperate condition, and because of the availability of the equipment and familiarity with its use, we elected to catheterize the infant's umbilical vein with a No. 17 gauge polyethylene catheter, and transfuse him with type O Rh-negative female blood which was also available. At 12:20 P.M., ten minutes following delivery, the infusion of blood was begun. After 20 c.c. of whole blood were given, a specimen was withdrawn from the umbilical catheter for counts and hemoglobin. (Previous attempts by the technician to obtain capillary blood were unsuccessful.)

The initial red blood count was 2.4 million per cubic millimeter with a hemoglobin of 11.0 Gm. per cent. The infusion was continued slowly over a period of two hours. A total of 136 c.c. of whole blood was given, and 27 c.c. were removed for counts and laboratory data. A dramatic clinical response was obtained and an apparently normal vigorous infant of good color was sent to the nursery. At the termination of the infusion of blood, 10 c.c. of calcium gluconate were given to help prevent the possible untoward effects of the large amount of citrate in the blood.

Laboratory data on the blood obtained from the catheter were as follows: total protein 4.2 per cent; albumin 2.9 Gm. per cent, globulin 1.3 Gm. per cent; calcium 10.5 per cent; and the icterus index was 12.6. The infant's blood type was determined to be type O, Rh positive. A complete blood count on the following day showed: red blood count 5.2 million per cubic millimeter; hemoglobin 15.0 Gm. per cent; white blood count 28,700 with a normal diffierential.

The baby's clinical course was uncomplicated. He was discharged home with his mother on the sixth postpartum day.

Summary

A case of infant exsanguination is reported. It is postulated that the descent of the baby near the end of the second stage with the short cord around its neck, had mechanically torn a small vein at the marginal insertion of the cord, with the resulting loss of fetal blood.

Treatment of an infant who has suffered an exsanguinating hemorrhage from vasa previa, ruptured velamentous insertions, or from the above mechanism, must be instituted even without knowledge of the cause of the blood loss.

The umbilical vein is suggested as the best route to institute such therapy. The technique is simple and the equipment necessary is minimal:

a. Blood is removed and replaced in 10 c.c. aliquots through a simple closed system consisting of a No. 17 gauge Diamond catheter (polyethylene tubing). The catheter is inserted a variable distance, 3 to 3½ inches.

b. The umbilical cord is cut approximately ½ inch from the cutaneous juncture.

It is the policy of the blood bank in this hospital to maintain a bottle of type O Rh-negative female blood in the blood bank at all times particularly for use in erythroblastotic infants.

ENTEROGENOUS CYST COMPLICATING PREGNANCY

WILLIAM G. LANGSTON, M.D., MARIANNA HOOD, M.D., AND ASA A. NEWSOM, JR., M.D., DALLAS, TEXAS

(From the Baylor Hospital)

THE recent report of Lovelady and Dockerty[1] on extragenital pelvic tumors has prompted this report of an enterogenous cyst in the pelvic cavity. Enterogenous or enteric cysts are considered to be developmental in origin, there being several theories as to their mode of development. Reports of these growths indicate that of all locations where they have been found, the pelvic cavity is probably the most rare. We have encountered reports of only six enteric cysts occurring in this location in both sexes, five of them posterior and one of them anterior to the rectum.[2, 3, 4, 5] No report of a pelvic enterogenous cyst complicating pregnancy has been found in a survey of the twentieth century literature.

The patient was a 21-year-old white para 0, gravida i. The last menstrual period was July 10, 1949. The expected date of confinement was April 15, 1950. Her past history was essentially noncontributory. There was no history of rectal or pelvic complaints. Physical examination on Sept. 22, 1949, reevaled no abnormality except in the pelvis. The cervix was slightly dusky, and the uterus was softened and enlarged to the size of an 8 to 10 weeks' pregnancy. Posterior to the rectum and between it and the lower sacrum and upper coccyx, lying largely to the right of the midline, was a tensely fluctuant, smooth, nontender mass estimated to be about 7 by 7 by 5 cm. There was practically no motility. Although the rectal mucosa could not be freely moved over the surface of the tumor, the wall of the mass and the rectal mucosa did not seem to be adherent. Through the proctoscope the rectum appeared normal. The blood Kahn test was negative, the hemoglobin was 12.4 Gm., the urine was normal. Weight was 131 pounds. The blood pressure was normal. An intravenous pyelogram showed a normal urinary tract. Anteroposterior and lateral x-rays of the bony pelvis showed no anomalies or evidence of bone destruction. The tumor mass was seen as a light shadow of a size and location similar to that noted at the time of initial examination. It was decided to defer removal of the mass until a time less provocative of abortion should be reached. On Jan. 4, 1950, removal of the tumor under spinal anesthesia was effected. The patient was placed prone on the table with a pillow under the upper thighs. A midline incision was made from just above the sacrococcygeal junction to the verge of the anus. The coccyx was removed and the incision was deepened. The lower pole of the tumor presented in the fat of the right ischiorectal space. It was dissected free by blunt dissection without difficulty. Although it was ruptured as the upper pole was being freed, the wall was easily distinguished from the adjacent tissues and removed without difficulty. The contents had the appearance of old pus but were odorless. No important nerves or blood vessels were encountered; the operation was almost bloodless. The wound was very loosely and incompletely closed over a soft rubber tissue drain. It healed uneventfully in about five weeks. The patient was out of bed on the day following operation and was discharged on the third postoperative day. The remainder of pregnancy was normal. After an uneventful labor, she was delivered by low forceps on April 20, 1950. A right mediolateral episiotomy healed by primary intention.

Pathologist's Report.—Submitted was a cystic structure measuring 2.8 by 1 by 0.8 cm. The outer surface was smooth and mottled and glistening. The cystic structure had been incised and there was evidence of a dark-staining, mucoid material present. The cyst wall

itself was smooth. The lining of the cyst was smooth and glistening with trabeculations. It also had a mottled appearance. Sections of the tissue submitted revealed it to consist of a fibrous and smooth muscle wall which was lined along one border by mucus-secreting columnar epithelium, which was stretched out in most areas in a single row of epithelial cells. A few small glands lined by the same mucus-secreting cells were noted in the submucosa. In one small area, pseudostratification was present. Just beneath the mucosa the aforementioned smooth muscle appeared to be circumferential, and peripheral to this some

Fig. 1.—Low power of wall of cyst.

fibers were seen which appeared to be cut end on. Beyond the smooth muscle was seen a fibrous connective tissue stroma throughout which were seen numerous lymphocytes and macrophages which contained a greenish-yellow pigment. Throughout the wall of this cystic structure there was an increased amount of collagenous connective tissue. There was no evidence of anaplasia. *Pathological diagnosis:* Enterogenous cyst.

References

1. Lovelady, S. B., and Dockerty, M. B.: Am. J. Obst. & Gynec. 58: 215, 1949.
2. McLanahan, S., and Stone, H. B.: Surg., Gynec. & Obst. 58: 1027, 1934.
3. Custer, B. S., Kellner, A., and Escue, H. M.: Ann. Surg. 124: 508, 1946.
4. Ladd, W. E., and Gross, R. E.: Surg., Gynec. & Obst. 70: 295, 1940.
5. Raven, R. W.: Brit. J. Surg. 23: 337, 1935.

4227 Herschel Street

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE, A REPORT OF TWO CASES

LAURENCE G. ROTH, M.D., BATAVIA, N. Y.

(From the Department of Obstetrics and Gynecology, The Genesee Hospital, Rochester)

SINCE primary carcinoma of the Fallopian tube is uncommon, this report of two cases is made. Stern and Hanley[1] have reviewed the 61 cases in the North American literature during the previous sixteen-year period and have reported 6 additional cases. Hu, Taymor, and Hertig[2] have recently reported sixteen cases. With the two cases reported here, the total number of cases of primary carcinoma of the Fallopian tube in the past seventeen years is 85. On the basis of these reports, the all-time total is 486 cases. However, this may be regarded as an approximation since many of the early reports did not clearly distinguish between primary and secondary carcinoma of the Fallopian tube.

CASE 1.—M. S., No. 105341, a 52-year-old white, married, para i, gravida i housewife, consulted her physician because of enlargement of the abdomen during the previous three weeks, urinary frequency and urgency for one week, and intermittent, sharp pain in the left hip radiating along the medial aspect of the thigh for one week. The last menses had occurred fourteen months previously, but the patient continued to complain of hot flashes and nervous instability for which she had been given injections of estrogenic preparations. She had always enjoyed good health except for a toxic thyroid adenoma which had been removed eight months previously after preparation with iodine and propyl thiouracil. Pelvic examination six months previously had been completely negative. Pelvic examination at this time revealed a palpable, smooth, cystic mass in the region of the left adnexa. A mdoerate, normochromic-normocytic anemia was present. General physical examination was negative except for evidence of moderate, generalized arteriosclerosis and mild hypertension

Because of the rapid onset of symptoms and growth of the mass, carcinoma of the ovary was suspected. The patient was admitted to the Genesee Hospital on Aug. 12, 1949, and a laparotomy was performed the following day. The left adnexal mass was revealed as a large, tortuous hydrosalpinx. The right tube was similar in appearance, although minimally involved. The ovaries and uterus were normal. During the exploration, the left tube was inadvertently ruptured, releasing a brown fluid containing golden, caseous particles. A bilateral salpingo-oophorectomy was done. The postoperative course was benign and the patient was discharged on the fifth postoperative day.

Pathological examination of the tissue revealed a papillary carcinoma of the left Fallopian tube with giant cells and some inflammatory cells, but no evidence of invasion. The condition in the right tube was diagnosed as endosalpingosis, no evidence of carcinoma being found. Both ovaries were unremarkable. With the diagnosis established, it was felt that the patient had a poor prognosis because of the limited surgery performed and especially in view of the spillage which had occurred at the time of resection.

The patient continued to be free of symptoms. Repeated, careful examinations failed to reveal any evidence of recurrence. On March 22, 1950, she was further treated with intrauterine radium, receiving a total of 4,500 mg. hr. Since then, the patient has been free of complaints. She has gained weight and is free of symptoms of the climacterium. When last seen on July 28, 1950, there was no evidence of recurrence.

CASE 2.—L. H., No. 115349, a 54-year-old white, married, para i, gravida i housewife was admitted to The Genesee Hospital on Oct. 4, 1949. The onset of right upper quadrant pain had been noted eight days previously. This was followed by progressive enlargement of the abdomen accompanied by dyspnea, orthopnea, anorexia, and occasional nausea, culminating in her admission for obvious ascites. The patient had been a known hypertensive for six years. During this period she had been given injections of an unknown nature intermittently to reduce weight and to decrease abdominal swelling. These treatments had previously been successful. Five months prior to admission, the patient noted

the onset of a thick, white leucorrhea, occasionally pink in color, and occasional postcoital spotting. Easy fatigability was noted and anemia diagnosed. Menses were absent for the first time in twenty-five years, three months prior to admission. Menorrhagia, the first menstrual abnormality, occurred two months prior to admission. Menses one month prior to admission were normal. The history was otherwise negative. The patient's father had died at 53 years of age of carcinoma of the stomach. The family history was otherwise negative execpt for hypertensive and vascular disease in her mother and two siblings.

On examination, there was hypertension with some cardiac enlargement, but no evidence of cardiac failure. There was obvious ascites. A mild anemia was present. Pelvic examination was unsatisfactory but revealed the presence of stony hard masses in the fornices. Electrocardiograms revealed only sinus tachycardia. A chest x-ray was negative except for "plate" atelectasis thought to be on the basis of insufficient aeration. X-ray studies of the abdomen revealed a normal gas pattern except for displacement by a rounded mass arising from the pelvis. The patient's course was markedly febrile despite the administration of therapeutic amounts of antibiotics. The impression was abdominal carcinomatosis, probably primary in an ovary.

In hope of facilitating palliative deep x-ray therapy, it was decided to explore the abdomen to remove the ascitic fluid, tumor mass, and omentum. Exploration was carried out on Oct. 8, 1949. About 4 L. of straw-colored ascitic fluid were removed. The entire abdominal peritoneal surfaces and the omentum were seeded with malignant nodules. A mass arose from the fundus to involve the left adnexa. There was a minimal hydrosalpinx on the right side. Subtotal hysterectomy, bilateral salpingo-oophorectomy and removal of the omentum were carried out. The procedure was well tolerated with supportive therapy. The postoperative course was mildly febrile but satisfactory until the recurrence of ascites was noted on the third postoperative day. Subsequently the ascites increased and the fluid output dropped to about 10 per cent of the intake. The course was progressively downhill. Paracentesis on the ninth postoperative day obtained 3,500 c.c. of fluid, but the patient expired quietly eight hours later.

Pathological examination of the surgical specimen revealed a primary carcinoma of the left Fallopian tube, varying from simple columnar epithelium to wildly growing anaplastic tissue. The predominant cell type was anaplastic with an admixture of cells with giant nuclei, frequently hyperchromatic and pleomorphic. There was invasion of the lymphatics of the left ovary, but the stroma was normal. The right tube and ovary were unremarkable. Complete post-mortem studies revealed carcinomatosis of all peritoneal surfaces with extension to the periaortic lymph glands and diaphragm, and direct extension to the liver.

During the period 1934 through 1949, there have been 96,509 admissions to The Genesee Hospital, of which 387 have been for primary malignancies of the female genital tract. Of these malignancies, there have been one case of secondary adenocarcinoma of the Fallopian tube, primary site in an ovary, and the two cases of primary carcinoma reported here. During this same period, there have been 50 cases of generalized abdominal carcinomatosis where the primary site was not determined. There have been one case of generalized abdominal carcinomatosis, primary site in the breast, and two cases, primary site in the gastrointestinal tract.

This experience suggests two things. First, early diagnosis and treatment are possible when both patient and physician act fortuitously in accordance with present concepts of preventive medicine. Second, the true incidence of primary carcinoma of the Fallopian tube is probably greater than appreciated.

References

1. Stern, Bruce D., and Hanley, Bernard J. Am. J. Obst. & Gynec. 58: 517, 1949.
2. Hu, C. Y., Taymor, M. L., and Hertig, A. T.: Am. J. Obst. & Gynec. 59: 58, 1950.

209 East Avenue.

STARCH SPONGE—A NEW HEMOSTATIC AGENT

SAMUEL S. ROSENFELD, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Departments of Obstetrics and Gynecology, The Jewish Memorial and Lebanon Hospitals)

HEMORRHAGE is at present acknowledged to be the leading cause of death in obstetrics. Therefore, any agent which possesses the property of arresting hemorrhage deserves serious study and consideration by all who either deliver or operate on patients.

In 1947 a patent was granted to Dr. Bice and Dr. MacMasters, and assigned by them to the U. S. Department of Agriculture for an absorbable starch sponge which could be utilized both as a food and a surgical dressing. After reading a description of this patent, it seemed to me that because of the chemical and physical composition of the substance that not only would it be useful for the purposes they had in mind, but that it would also act as a hemostatic agent.

The dry sponge is capable of absorbing sixteen times its weight in water. It can absorb appreciable amounts of medicaments such as penicillin, streptomycin, gramicidin, and sulfonamides, etc. The idea of the patentees was to incorporate medicinal substances into the sponge and introduce them into deep or surface wounds where they could be left until absorbed. The sponge disintegrates slowly in body fluids and the dissolved material after enzymatic attack is absorbed by the tissues without harmful results.

Bice and MacMasters[1] describe the preparation of the sponge as follows: Make a "slurry" of starch in water. This usually contains 5 to 10 per cent of starch by weight. In general, the higher the concentration of starch the finer the texture of the sponge. At equal concentrations, cornstarch makes a firmer sponge than wheat or potato starch. Additions of chemicals that are to be incorporated into the sponge may be made to the "slurry" or to the paste.

Sponge formation is brought about by slowly freezing the paste. Freezing must be complete throughout the paste before thawing is permitted.

After thawing is completed, the sponge is squeezed or pressed to remove free water. If it is to be used wet, the material is stored in 70 per cent ethyl alcohol.

The dry sponge is sterilized by cutting it into the desired size and shape, and may conveniently be wrapped in heavy paper and tied with a string. These wrapped pieces may then be placed in a container and autoclaved.

The sponge must immediately be dried, which is accomplished by drying under vacuum in the autoclave, or by subjecting the sponge to a temperature of 90° C. in a drying oven for at least one hour.

The Engineering and Development Division of the Northern Regional Research Laboratory estimated in 1945 that the actual cost of producing the sponge exclusive of the cost of the starch, administration, and selling expenses would be 9.48 cents per pound in a plant with a capacity of one ton of starch a day, and 6.67 cents in one with a daily capacity of five to ten tons. Due to increased prices of materials and labor, the production costs in 1950 would undoubtedly prove to be higher.

The starch bar as seen microscopically is a spongelike structure with extremely tiny cells and threadlike or fibrous walls, and it retains this form after soaking in water.

Starch powder consists of flat plates with irregular outlines, occur in small clumps, and when wet appear to increase 10 to 20 times in diameter, but retain their form and become more transparent.

In the majority of cases I found it most expedient to employ the bar of starch sponge. In some cases, such as after cauterization of the cervix or after circumcision, the ground starch sponge or powder is preferable. In postpartum and in rectal cases I have found the impregnated starch sponge bandage to be more desirable than the bar.

Lee and Lehman,[2] in searching for a substance to replace talc which at times is responsible for the appearance of granulomatous growths, found a cornstarch derivative which proved very satisfactory. This starch product replaces talc which is ordinarily used in operating rooms for the preparation of surgeons' rubber gloves. These authors stated, "The fate of this powder (starch) does not offer any great pharmacological problem. Since it is a cornstarch powder, it is simply taken up by the peritoneum and metabolized like any ingested starch."

They quoted MacQuiddy (personal communication), who investigated the sensitizing properties of this substance both in human patients and in animals, and failed to demonstrate any sensitizing or anaphylactogenic properties.

Lee and Lehman, in experiments with the cornstarch product described in their article, showed complete absorption from the peritoneum without any demonstrable inflammatory reaction, and further stated that it produces no adhesions whatsoever.

MacQuiddy and Tollman,[3] in an article entitled "An Absorbable Powder to Replace Talc," reported the satisfactory use of a cornstarch derivative treated by physical and chemical means to improve its lubricating value and to prevent gelatinization when autoclaved.

Correll, Prentice, and Wise[4] reported that starch implants in the muscles of rats could not be identified by gross inspection after the tenth day. The stained specimens revealed fragments of starch through the fiftieth day. No significant tissue reaction to this material was observed, but the forty- and fifty-day specimens revealed an extraordinary cellular infiltration, largely of mononuclear phagocytes. The type of phagocyte that usually engulfs lipoids seems to be attracted by this material invading and replacing it.

Although our problem was more concerned with hemostasis than with adhesions, nevertheless we performed experiments to determine the action of starch in the presence of hemorrhage and its effect on the peritoneum. The employment of even a markedly efficient hemostatic agent that produces crippling adhesions would indeed only be justified in the direst emergency. Fortunately this did not prove to be the case when starch sponge was used.

I found the sponge to be an excellent hemostatic agent in the rabbit. Experimental animals survived in whom I incised either the large veins of the ear, the femoral vein, or the inferior vena cava. In the case of the auricular or femoral veins the fellow of the opposite side was used as a control. The vena cava experiments were controlled by administering no treatment to some of the control animals, and treating others with pressure and gauze packing.

All the untreated animals, as expected, died within one to two minutes after the vena cava was incised.

When plain gauze was pressed against the opening in the vena cava and left in situ as a pressure pack, hemostasis resulted. When these animals were autopsied approximately one month after operation, the adhesions encountered

were so dense and the intestines so compromised that at present with the ready availability of efficient hemostatic agents the practice of employing plain gauze as a packing in cases of hemorrhage should be abolished, except in those instances where no other suitable hemostatic substance can be obtained. Another drawback to the gauze pack is its tendency to disturb the clot and tear tissues on removal so that bleeding commences again.

In every case where the starch was properly applied to any of the venous structures mentioned previously, including the vena cava, the animal survived.

We found that the best method of obtaining hemostasis with the starch sponge was to moisten one end of the dry starch bar with sterile water or saline solution, and to cover the opening in the vein with this moistened end, simultaneously creating pressure by bearing down on the dry end of the bar. When all bleeding ceased, usually a matter of one to two minutes, the whole or part of the bar was left in situ.

Large pieces of starch were left in the peritoneal cavity of some animals so that the effect of massive pieces of starch sponge could be studied.

Taking into consideration the fact that the vena cava is located in the retroperitoneal space, the cellular tissue of which is almost embryonal in its reaction to stimuli such as irritants, foreign bodies, etc., the adhesions we found at autopsy, usually performed three to four weeks after operation, were surprisingly moderate.

To study the reaction of the general peritoneal cavity to the sponge rather than that in the retroperitoneal space, I introduced large pieces of dry and wet sponge among the intestinal coils without opening any large vessel. At autopsy, gross inspection in the majority of these animals revealed none or minimal adhesions. One animal, however, showed a walled-off sac attached to one of the intestinal coils. Another animal showed a small granulomatous lesion in the lower angle of the peritoneal incision. It should be taken into account that much more starch was used in these animals than would ever be found necessary to employ in a human being weighing many times more than the experimental animal. All of these animals survived, appeared healthy, and had gained in weight in the three- to five-week interval between operation and autopsy. Frantz,[5] in discussing Oxycel, stated that cysts are sometimes found in serous cavities where a relatively large mass of material is surrounded by serous membranes. Such cysts usually resorb.

I have up to the present employed starch sponge either in the form of the bar, the powder, or the gauze pack in 155 instances. Table I shows the types and number of cases so treated:

TABLE I.

Cesarean section	26	Dilatation, curettage and biopsy of cervix	8
Cesarean hysterectomy	1	Interposition operation	16
Postpartum hemorrhage	3	Manchester operation	16
Salpingectomy	3	Laceration of vagina	1
For rupture of a hemorrhagic corpus luteum cyst of pregnancy	1	Postoperative vaginal hemorrhage	1
Resection of ovarian cysts	3	Resection of Bartholin's gland	1
Resection of presacral nerve	1	Hemorrhoidectomy	5
Hysterectomy, abdominal	36	Rectovaginal fistula	1
Hysterectomy, vaginal	13	Excision of fascia lata	3
Myomectomy	5	The Mohalim (Ritual circumcisers) have used starch powder in several hundred ritual circumcisions.	
Amputation of cervix	2		
Cauterization of cervix	9		

Two patients presented themselves in such a way that control observations were possible.

Case Reports

CASE 1.—This patient had had a splenectomy at the age of 12 years because of thrombocytopenic purpura. Her history indicated that she had had a very difficult first labor and delivery and was given an infusion of plasma immediately post partum. On the basis of this history the obstetrician had taken the precaution of giving her blood transfusions before and after delivery and packing the uterus tightly with plain gauze. Despite these precautionary measures a severe hemorrhage ensued, and she exhibited many of the signs of and symptoms of impending death. The gauze pack was removed and a starch sponge introduced. The bleeding ceased almost immediately, and she was discharged from the hospital on the eleventh postpartum day.

CASE 2.—This 70-year-old woman had a prolapse of the uterus, and had worn a pessary for many years. Her doctor removed the pessary because of pressure symptoms, and after several weeks an attempt was made to reinsert it. Great difficulty was encountered and attempts at reinsertion were abandoned. However, the vaginal walls had sustained multiple lacerations, and copious bleeding took place. Several vaginal packings of plain gauze proved ineffectual. She was admitted to the hospital where a gauze pack was removed and starch sponges substituted. Impregnated starch gauze packing was at that time not yet available and starch sponges were therefore introduced into the vagina, the sponges being maintained in position by placing a small amount of gauze in the vaginal orifice external to the outermost sponge bar. The bleeding was promptly controlled.

CASE 3.—Another case in which starch sponge yielded a most gratifying result concerned a 52-year-old woman who had had an intrauterine insertion of radium five years previously because of menorrhagia. She had been suffering from colitis for many years. She was admitted to the hospital almost exsanguinated and in extremis, about one week after discharge from the hospital where a plastic operation had been performed for the repair of a cystorectocele. Numerous bleeding points were seen, but the tissues were so friable that clamps could not stay in place, and suture material tore right through. The vagina was tightly packed with bars of starch sponge and starch gauze, and the bleeding ceased. The patient was transfused while the operation was in progress. Convalescence was uneventful. This patient's chronic colitis probably had some effect on her blood clotting mechanism.

Seegers and Sharp[6] state that acacia changes the reactivity of purified fibrinogen very markedly. A solution containing 2 per cent acacia will clot in fifteen seconds with half as much thrombin as is required when no acacia is present. The favorable effect disappears in solutions stronger than 7 per cent. The results I otbained with 1 per cent and 2 per cent solutions of starch sponge resembled the findings of Seegers and Sharp. I found that in these dilutions a blood clot is obtained with one-third less thrombin than would normally be required.

After observing the action of the sponge in gynecologic operations, members of the Genito-Urinary and Otolaryngological Services at both Lebanon and Jewish Memorial Hospitals are now employing starch sponge as a hemostatic agent. The genitourinary staff is loud in the praise of the starch sponge pack in prostatectomy cases where it not only controls bleeding, but possesses a very great advantage in that its removal is painless. My experience in removing intrauterine and vaginal packs is similar to that of the Genito-Urinary Service. The reason for the lack of pain on removal is due to the fact that the starch sponge lubricates the gauze, thus preventing the adherence of gauze to tissue. The otolaryngologists in their tonsillectomies insufflate sponge powder into the tonsil fossa. The Mohalim dust the powder on the circumcision wound.

When operating in areas where a clamp or suture can injure important structures, such as the ureters, bladder, large blood vessels, nerves, etc., it is

indeed comforting to have an agent at hand which is capable of controlling oozing without recourse to clamps or sutures.

The Medical Services have administered solutions of starch sponge powder orally in cases of hemorrhage from esophageal varices and in bleeding gastric ulcer. The effects were encouraging, but the series is too small to permit of valid conclusions.

There was no mortality in this series. There was one morbidity that might have possibly been due to the intrauterine introduction of starch sponge. This occurred in a patient who had retained secundines and continued to bleed after curettage. The uterus was packed with starch sponge. A few hours after operation her temperature rose to 105° F. One cannot be certain that the starch sponge was the responsible agent, for she received a blood transfusion, and in addition the possibility of intrauterine infection could not be excluded. Both of the latter possibilities are competent producing causes for the reaction that this patient exhibited, and either or both might have been the cause. The patient left the hospital in good condition on the fourth postoperative day.

The action of starch sponge seems to be a local one. It absorbs many times its weight in blood. This causes the sponge to swell and to exert pressure, thus forming a mechanical obstruction to the flow of blood. The adhesive properties of the sponge may also play a role in imposing the mechanical barrier. Retardation of flow affords the clotting mechanism more time in which to effect a clot and clotting is further facilitated by reason of the fact that in the presence of starch sponge, one-third less thrombin is required for clot formation.

Summary and Conclusion

Starch sponge was employed as a hemostatic agent in 155 cases. The starch was applied either in the form of a bar, a gauze impregnated pack, or as a powder. Intraperitoneal, intrauterine, vaginal, perineal, rectal, fascial, and muscle applications were made.

In nearly every instance where oozing of blood resulted from capillary or venous injury, hemostasis was attained.

The action of the sponge is apparently local and augmented by the fact that less thrombin is required for the formation of clot.

The low cost of the starch sponge in comparison to other hemostatic agents such as Gelfoam, Oxycel, etc., is a real contribution in this era of high cost of medical care.

I wish to thank Dr. M. M. MacMasters of the United States Department of Agriculture and her staff for their fine cooperation, Dr. B. Lapan for his invaluable assistance, Drs. A. A. Angrist, J. C. Ehrlich, S. Brodie, and A. Schwarz for examination of tissue and valuable suggestions, and Miss Beatrice Ferrill, R.N., for ingeniously preparing starch sponge bandage.

References

1. MacMasters, M. M., and Blom, R. H.: The Chemurgic Digest 37: December 15, 1945.
2. Lee, C. M., Jr., and Lehman, E. P.: Surg., Gynec. & Obst. 84: 689-695, 1947.
3. MacQuiddy, E. L., and Tollman, J. P.: Surgery 23: 786-793, 1948.
4. Correll, J. T., Prentice, H. R., and Wise, E. C.: Surg., Gynec. & Obst. 81: 585-589, 1945.
5. Frantz, V. K.: Hemostatic Agents, in Seegers, W. H., and Sharp, E. A.: Springfield, Ill., 1948, Charles C Thomas, Publisher.
6. Seegers, W. H., and Sharp, E. A.: Hemostatic Agents, Springfield, Ill., 1948, Charles C Thomas, Publisher.

1882 Grand Concourse.

Department of Book Reviews

EDITED BY PHILIP F. WILLIAMS, M.D., PHILADELPHIA, PA.

Review of New Books

In the Experimental Laboratory of Histophysiology attached to the Department of Gynaecology of Brugmann Hospital, under the inspiration and direction of Professor R. Bourg, the author has not only re-enacted the already known cytological techniques on vaginal and cervical smears, and applied them to the clinical diagnosis and treatment of patients, but he has developed a number of personal techniques. The results of his research compare favorably with the statistics of other clinics.

The reason that prompted the author to publish his findings[1] is to expose to the clinician the biological bases of the method; that is why the first part of his book exposes the histophysiology of the vaginal mucosa.

The various colored illustrations are detailed to make it easy for those interested in laboratory work to find all useful indications.

What was lacking most up to the present time were the clinical bases as applied to the method. No book exists which includes the information obtained in the study of pathological cycles. This work stresses particularly by clinical experimentation and the study of patients the cytological modifications in the course of the anovular, the hypo- and hyperfollicular cycles and the cytological characteristics in the ovulatory phase.

This could be achieved only through the observation of the particular cytological reactions of smears under the influence of estrogens, of progesterone, and of testosterone. There were derived therefrom the very simple bases for the control of hormonal therapy in gynecology, for the practical application of artificial insemination, and, moreover, for the application of hormonal treatments in mammary and genital carcinomas.

In applying the technique to smears collected from the cervix in sterility, Huhner's test, of prime importance in such cases, has, by it, been perfected and rendered more precise.

The very live question of the diagnosis of cancer and of precancer of the genitals by the study of smears is envisaged in a very objective manner, with all the difficulties of the examination and all the criticism that has been made of it taken into consideration; also, the progress which has been made up to the present time and all which should naturally develop in the future by this new method. There is a direct relation between the question of precancer and the genital smears. This method should allow the clinician to suspect a lesion at its onset, and modify his attitude in perfecting his diagnosis before the cancer has invaded the tissues too extensively.

Colored photographs presented as a supplement to the book constitute a folder permitting a constant reference to the cytological evolution as described in the text. Graphs and illustrations are numerous. The bibliography covers 23 pages in small print, giving to the book a considerable value from an informative point of view.

The biologist, the general practitioner, the researcher, the gynecologist, the endocrinologist, and the cancerologist will find in it a source of reference and of interesting data of unsurpassed value.

LÉON GÉRIN-LAJOIE

---

[1] **Les Frottis vaginaux et cervicaux, bases biologiques et cliniques. (Vaginal and Cervical Smears, Biological and Clinical Bases.)** By J. Paul Pundel, Laboratory of Experimental Histophysiology, attached to the University Department of Gynecology of Brugmann Hospital, of Brussels, Belgium, under the direction of Professor R. Bourg. 350 pages with 82 illustrations and numerous graphs; Paris, 1950, Masson & Cie. 2000 French francs (about $7.00).

The third edition of **Nursing in Prevention and Control of Tuberculosis**[2] is a painstaking revision designed to familiarize nurses with the treatment and prevention of this disease. The book is well planned and clearly written with free use of excellent illustrations and statistical tables to clarify points made in the text and aid in memorizing the facts presented. Special emphasis is laid on case finding, tuberculin testing, the use of the various antibiotics, BCG, and surgery, as well as the nurse as a teacher in the prevention and control of tuberculosis. The questions and list of references at the end of each chapter with the outlines for the doctor and nurse in the preparation and presentation of case histories make the book a valuable asset to the student.

Although the authors' viewpoint is frankly that of the public health worker, one wishes that they had considered the patient more as an individual than as a case and that more attention were given the psychological and emotional aspects of the disease. One gets the impression that they are more familiar with the management of clinic patients than of those who have actually been hospitalized for tuberculosis. From a practical standpoint, the hospital administrator might well complain that some of the techniques suggested are needlessly expensive (three gowns per nurse per day) and the use of gauze masks with paper filling and tape strings when plastic masks can be obtained at less cost. While frequent handwashing is emphasized and a basin of running water is suggested for each room, contaminated and uncontaminated areas are not clearly defined. Sputum cups are considered unsatisfactory and the use of paper handkerchiefs for expectoration is recommended although the latter are untidy and objectionable because they do not give the physician and nurse an opportunity to observe the type and amount of sputum and whether or not it contains blood. One would also like to see a more adequate discussion of diet for tuberculosis patients, especially when complications are present.

The book will be of special interest and value to Public Health workers although it can be read with profit by every physician and nurse who wishes to broaden his general outlook on tuberculosis and become conversant with the methods of prevention of the disease among contacts and in families.

EDWIN M. JAMESON

This work[3] by Boeminghaus, formerly Professor of Surgery and Urology at the University of Berlin, comprises three slender volumes each of approximately 230 pages. The first volume deals with surgery of the kidneys and ureters, the second with surgery of the bladder, prostate, seminal vesicles, testes, vas deferens, and scrotum; and the third, with miscellaneous conditions and neurosurgical procedures related to diseases of the genitourinary organs. This division into three small volumes is a departure from the customary single volume in which the text could have been contained but it appears to have some practical advantages. The customary list of references is lacking in this publication, although authorities are quoted in the text. Also wanting is an index of authors at the end of the book. The author's idea was to make these volumes handy and practical.

In the main, his own experience and practice form the basis of the text, which the author justifies wherever differences with other authorities arise. Indications for the surgical procedures are particularly stressed, because they frequently change in the course of the changing phases of diseases of the genitourinary organs. Where there is a choice of several methods of attack, the author enters more fully into the pros and cons for preferring his own.

The book is adequately illustrated from sketches prepared by the author himself. In most cases, they are too dimensional, but present the important details of technique. The material covered is complete as far as concerns the surgical requirements of this special field.

---

[2]**Nursing in Prevention and Control of Tuberculosis.** By H. W. Hetherington, M.D., M.R.C.P. (London), Chief of Clinic of the Henry Phipps Institute of the University of Pennsylvania, and Fannie W. Eshleman, R.N., B.S., Supervisor of Public Health Nursing of the Henry Phipps Institute of the University of Pennsylvania, Lecturer on Tuberculosis Nursing, Department of Nursing Education of the University of Pennsylvania. Revised Third Edition. 361 pages with 12 illustrations. New York, 1950, G. P. Putnam's Sons..

[3]**Chirurgie der Urogenitalorgane.** By H. Boeminghaus, Professor of Surgery and Urology, University of Berlin. 690 pages, illustrated. Bad Worishofen, 1950, Edmund Banaschewski.

Conspicuous is the lack of adequate reference to chemotherapy and antibiotic therapy which have played so large a part in the successful manangement of surgical conditions of the genitourinary system. Here and there scant mention is made of these newer drugs without any specifications for their use. Little attention has been given to preoperative preparation and postoperative treatment. These items would not conceivably be omitted in any American book on surgical procedures. The author frankly states that he did not wish to burden the reader with too much detail. Aside from these omissions the book nevertheless serves as a useful compendium of urological surgery for general surgeons and gynecologists, as well as urologists.

I. C. RUBIN

This monograph[4] is an interesting correlation between physiology, pathology, and clinical medicine. The author is convinced that there is no disease which would be localized in one organ, but, through intricate nervous and hormonal connections, the entire organism is affected. This pathophysiological relationship is illustrated in various organs of the body, discussed in the 12 chapters of the book. The book is divided into 14 chapters; the first chapter is an introduction and the last consists of concluding remarks. The chapters dealing with the disturbances of circulation, respiration, blood formation, and particularly the nervous regulations and internal secretion, are well treated and contain much up-to-date information, thus reflecting the special interest of the author in these topics. The pathophysiology of the gonads is given briefly, and pregnancy and complications of pregnancy, such as anemias and nephropathies, are mentioned only in outline form. Unfortunately, no detailed numerical list of references is given, and the author gives only selected monographs as the source of his information.

JOSEPH STASNEY

The Clinical Use of Testosterone[5] is a sharp, concise review of this subject. Following a brief introduction, the chemistry of these steroids is adequately explained to us in just two pages. The basis for treatment is brought out in the chapters on physiology and metabolism and, as is appropriate in this case, considerable space is devoted to the human male. Both here and in the section on therapeutics an important background of fact is developed which is essential to the intelligent use of the androgens in our specialty. The author is always careful to discriminate between the situations in which these drugs have an established value and those in which their use is questionable or potentially dangerous. A section on commercial preparations, and an up-to-date addenda with bibliography complete the work.

There are warmth and humor in this excellent presentation which make it enjoyable as well as profitable reading.

JOHN D. CORBIT, JR.

This highly technical volume, **Hormone Assay**,[6] as its name implies, deals with the various methods used for the assay of vertebrate hormones. Eighteen collaborators including the editor have contributed an outstanding work in its field. A concise lucid initial section is fittingly devoted to the practical aspects of statistical methods and the interpretation of data. There follow nineteen sections each of which is essentially a monograph on the assay of a specific hormone or related hormones. The practical use of the volume is considerably enhanced by a full table of contents and bibliography that are incorporated into each section.

---

[4] **Klinische Physiologie und Pathologie.** By Prof. Dr. Ferdinand Hoff, Director of the Medical Clinic at the City Hospitals at Aachen. 782 pages, 124 illustrations, Stuttgart, 1950, Georg Thieme, Price: 39 D.M.

[5] **The Clinical Use Of Testosterone.** By Henry H. Turner, M.D., F.A.C.P., Clinical Professor of Medicine. School of Medicine, University of Oklahoma. 69 pages, with 12 illustrations. Springfield, Ill., 1950, Charles C Thomas. $2.25.

[6] **Hormone Assay.** Edited by C. W. Emmens, Department of Veterinary Physiology, University of Sydney, Sydney, Australia. 556 pages with charts, graphs, and illustrations. New York, Academic Press, Inc., $10.00.

As pointed out by the publishers **Hormone Assay** does present under one convenient cover practically all the biological and chemical methods for assaying hormones. More important, however, is the fact that the methods of assay are described in minute detail. Illustrations are frequently encountered in the text to explain techniques or show equipment. In most instances the prospective assayer needs little if any additional information beyond that offered in the text. Interpretation of the acquired data is simplified considerably for the worker by a profusion of pertinent tables, graphs, and charts. Of further value are the writers' critical comments on the various assay methods.

The most carping critic of the volume might cite the fact that the ground covered does not include work done within the past year or two. This objection is valid because the literature continues to be burdensomely replete with contributions pertaining to hormones. Included in the latter are many noteworthy additions to the field of hormone assay. Unfortunately, a lag is inevitable in practically all scientific books. The degree of deficiency is proportionate to the activity in the field and becomes particularly apparent in a volume such as the one under present consideration.

In spite of the foregoing inadequacy, **Hormone Assay** possesses sufficient merit to justify giving it a prominent place in the library of those interested in hormone assays. Frequent revisions to include the most recent developments would add immeasurably to the volume's worth and might earn it a universal acceptance as the *vade mecum* of hormone assays.

RALPH B. WOOLF

A symposium on **Toxemias of Pregnancy,**[7] both human and veterinary, was held in London, January, 1950, under the auspices of the Ciba Foundation. The objective was to assemble all facts in physilogy, pharmacology, pathology, endocrinology, biochemistry, and obstetrics pertinent to the problem of the toxemias of pregnancy. The participants in this program were predominantly from the British Isles, but included some from Sweden, Holland, Switzerland, and the United States. Notwithstanding the diverse theories and opinions expressed, there was no attempt on the part of the symposium, as a whole, to promulgate or discredit any particular theory. The book is a collection of the papers presented at this symposium.

Since a solution of the problem of the so-called "toxemias of pregnancy" obviously requires the combined efforts of investigators in various fields, the task of a reviewer of this symposium is thereby rendered increasingly difficult. An obstetrician, however, may be better able to correlate the significant data, due to his familiarity with the clinical aspects of the problem. It is to be expected that his own researches will influence his review to no little degree.

The term *toxemias of pregnancy,* in the light of our present knowledge, is another example of "the perpetuation of error" as was so aptly expressed by Dr. Norman Miller in regard to medical teaching and writing.

The reviewer is convinced there is but one toxemia of pregnancy—that which is due to degeneration of chorionic epithelium. Inclusion of renal diseases and hypertensive vascular disease is in error since these are only predisposing causes. Eastman, in his recently published textbook, has almost, if not quite, corrected this particular error.

Considering the fact that the presence of chorionic tissue has come to be recognized as the basis for the development of toxemia of pregnancy, it is indeed strange that pathologists, while carefully noting general pathologic changes, have neglected to study the placenta.

Young was the first obstetrician to show the relation of placental infarction to toxemia of pregnancy. Some few obstetricians have completely substantiated his work, although holding different ideas as to the mechanism by which infarction is initiated.

---

[7] **Toxemias of Pregnancy.** Edited by Dr. J. Hammond, School of Agriculture, Cambridge; Professor F. J. Browne, Professor Emeritus of Obstetrics and Gynecology, London, and G. E. W. Wolstenholme. 280 pages, 93 illustrations, London, 1950, J. & A. Churchill, Ltd.; Philadelphia, 1950, The Blakiston Company. $4.50.

The essence of toxemia of pregnancy lies in infarction of the placenta, but a few pathologists, and many obstetricians in particular, still discredit this essential fact. Falkiner, late Master of the Rotunda, in Dublin, in emphasizing this fact, admonished us to "investigate this matter afresh and with an open mind." To the reviewer, it would seem much more difficult for the one who has already *seen* the evidence, to *un-see* it, as it were, than for those who have failed to recognize the evidence, to learn to do so.

As to general pathological effects, there is agreement on the evidences of vascular damage, increased capillary permeability, as amplified by Dieckmann in relation to salt and water balance, hemorrhages, and the effects of vasospasm.

Schneider emphasized the widespread dissemination of fibrin thrombi induced by the excess thromboplastin of placental necrosis and designated the resulting pathological effects as those of vascular occlusion rather than of a toxic nature.

To the reviewer, the fundamental concept of toxemia of pregnancy would seem to be akin to any condition in which there is mass degeneration of tissue within the body, the poisonous products of which have access to the general circulation, as in severe burns, crush injuries, and acute yellow atrophy of the liver. In toxemia of pregnancy, the etiological factor is localized degeneration of the placenta. The effects are peculiar to the chemical characteristics of placental tissue, namely, a very high thromboplastin content which induces formation of fibrin thrombi; a very high arginine content from which guanidine could be derived and account for convulsive and pressor manifestations, and histidine, a possible precursor of histamine which, in massive infarction, may be produced beyond the ability of histaminases to neutralize. In addition to these are the widespread damaging effects of vasospasm, likewise of possible guanidine origin. It has not as yet been possible to identify guanidine and histamine in the blood of toxic patients.

While the harmful effects of dietary deficiencies on the liver and hormone balances were admitted, there was general disinclination to attribute toxemia of pregnancy to dietary causes, as held by Theobald, who stated, "Eclampsia represents a breakdown in physiological mechanisms and there is no need to postulate a toxin."

Bastiaanse advocated the theory of placental ischemia and degeneration due to factors which interfere with sufficient blood reaching the placental area.

Such a factor would necessarily be of slow development and gradual in its effects and while this might agree with toxemia of slow progression, it hardly fits the acute fulminating cases.

The status of hormone imbalance in relation to toxemia of pregnancy received well-merited and full discussion. The high chorionic gonadotropin and low pregnandiol and estrogen values preceding the development of toxemia of pregnancy, as found by Smith and Smith and Priscilla White, while impressive, were at times variable or absent. "It should be said without discredit to their theory that much of the evidence which they advance is, as yet, circumstantial." To the reviewer, the results of their work are such as to insure them an important part in the solution of the problem.

As to any conditions in veterinary practice which simulate toxemia of pregnancy, one gains the impression that pathological states which affect cattle or ewes, near term, are clinically and pathologically unrelated to toxemia in the human being and are due to dietary causes.

In the reviewer's opinion the researches of Kapeller-Adler on histidine excretion and the evidence of histaminase activity in normal and toxic pregnancies are of basic and fundamental importance, and will add to the evidence already at hand, that abruptio is a histamine manifestation and not a condition apart from toxemia.

This book, representing, as it does, the most recent thought on toxemia of pregnancy, should be of interest and value as a reference work not only to those engaged in research on this problem, but to obstetricians in general. It is the reviewer's opinion that progress in the solution of the problem of toxemia is now being measured in months rather than decades and that symposia, as represented in this book, will prove to be an important factor in hastening the day.

R. A. BARTHOLOMEW

The public is anxious to read about their "conditions." There is seldom a magazine published lately which does not contain at least one article dealing with disease or physiology, not to mention the number of books on medicine for the laity which are legion. In a recent issue of the *New York Times Book Section*, a book for expectant mothers was mentioned along with such "best sellers" as *Mrs. Wiggs of the Cabbage Patch* and *Alice in Wonderland*, as a perennial best seller.

The fact is well established therefore that the pregnant woman of today wishes to be informed. Such another medical book for the laity is **To Prospective Mothers.**[8] According to the publisher's note, this book "is an attempt by two obstetricians to present to all expectant mothers the normal physiology of pregnancy and childbirth." The reader is soon jolted from the expected text to read in the Foreword, among others, this incongruous statement. "No longer may childbirth be regarded as a purely normal function. With the increase in the size of the fetal head there is a corresponding increase in the hazards of childbirth."

Throughout the text there are many statements which are not completely acceptable to most obstetricians. As an example one reads on page 113, "Lightening—the uterus settles forward and downward into the brim of the pelvis," and again on page 114 (rupture of the bag of waters), "which indicates the cervix is almost completely dilated."

It is the opinion of this reader that **To Prospective Mothers** needs a great deal of editing before it can be recommended.

MARIO CASTELLO

This[9] is a very readable discussion of pregnancy, labor, and delivery designed to explain the concept of natural childbirth for the expectant mother. The ideas are well presented and it appears an excellent manual for the use of any prenatal patient. The picture text is well done and adds materially to the book.

Such a sane presentation of a subject widely presented in the lay press is timely. The viewpoints which are presented should make the practice of obstetrics simpler for any physician whose patients read it whether he is an enthusiast for natural childbirth or not.

CARL P. HUBER

This book[10] furnishes a complete discussion of care during pregnancy for the patient who hopes to experience natural childbirth. Detailed instructions concerning the expectant parents' part in this regime are given. The first chapters appeared somewhat pedantic and by their tone limit the usefulness of the book to patients of physicians who are disciples of natural childbirth.

The manual is well written and adequately illustrated.

CARL P. HUBER

---

[8]**To Prospective Mothers.** By William E. Hunter, M.D., F.A.C.S., and Bernard H. Smith, B.A., M.D., Attending Obstetrician and Gynecologist, Saint John's Hospital, Santa Monica, Calif. 161 pages with 12 illustrations. Boston, 1950, Bruce Humphries, Inc., $2.50.

[9]**Understanding Natural Childbirth.** By Herbert Thoms, M.D., in collaboration with Laurence G. Roth, M.D., with a picture story by David Linton. 112 pages, illustrated. New York, 1950, McGraw-Hill Book Company, Inc.

[10]**Natural Childbirth.** By Frederick W. Goodrich, Jr., M.D., 168 pages, illustrated. New York, 1950, Prentice-Hall, Inc.

Correspondence

Inflatable Tips for Trigger Cannulas

To the Editor:

In the September number of this JOURNAL, Dr. E. Kahn writes on "An Inflatable Tip and Other Modified Interchangeable Tips for the Trigger Cannula Used in the Study of Female Sterility," in which he describes the adaptation of the Rubin-Myller cannula to his trigger cannula. His summary contains the statement, "that a new inflatable tip for intracervical obturation is described with a technique for its use in a self-retaining manner with or without the traction tenaculum."

Kahn emphasizes certain advantages of his cannula over the Rubin-Myller cannula. I should like to call attention to the fact that the advantages claimed by Kahn for his instrument are precisely the same as those offered by the Rubin-Myller cannula and that his is not a new cannula tip. The only claim for a new modification, if one can call it that, is that Kahn's inflatable tip is detachable; this is an adaptation made necessary by reason of the many uses to which the trigger cannula is put. Kahn also emphasizes the importance of a "simple valve." This same valve is incorporated in the handle of the Rubin-Myller cannula, reducing its weight and simplifying its manipulation. As leakage is one of the main sources of error in performing the Rubin test, an additional connection between the trigger cannula and its multiple tips serves only to increase this possibility.

The alleged advantages of Kahn's modification are repetitions of facts published in the original article of Rubin and Myller and as contained in the separate description accompanying their cannula. The principle of the inflatable cannula is quite old, having been devised by the inventor of the cystoscope, Nitze, about 70 years ago. The "trigger" idea was utilized by Windler as far back as twenty years ago.

ERNEST MYLLER, M.D.

65 EAST 76TH STREET
NEW YORK 21, NEW YORK
NOV. 8, 1950

Reply by Dr. Kahn

To the Editor:

It is apparent from the reaction to the word "new" in the summary of my article, "An Inflatable Tip and Other Modified Interchangeable Tips for the Trigger Cannula Used in the Study of Female Sterility" (AM. J. OBST. & GYNEC. 60: 692, 1950), that Dr. Myller, obviously, did not study the paper in its entirety. For if he had, he would realize, without offense, that the word "*new*" refers to a "*new*" member in the family of modified tips (with due credit given the inventors) used with the self-retaining trigger cannula.

In his letter he does not mention that I discussed and demonstrated every point of modification of the inflatable cannula personally with him and Dr. Rubin long before the article appeared and he did not object to the correctness of the claims set forth.

Whether the modifications provided in the inflatable tip, when used with the trigger cannula handle and traction tenaculum or independently are "advantages," only time and use should determine. It is unfortunate that Dr. Myller feels that the valve on the modified inflatable tip and the Rubin-Myller inflatable cannula are one. Further in-

vestigation on his part would reveal that his basic contribution to cervical obturation with an inflatable cannula is the three-way valve which is operated with a revolving disc marked B, C, X, and R. The inflatable tip for the trigger cannula, it should be noted, has an independent system of inflation and deflation, employing a standard type valve (pet cock) to control the volume of the balloon. This provides a simple means for inflating the balloon without the cannula slipping out of the cervix, and for adjusting the balloon volume during the Rubin test without interrupting the procedure.

The inflatable tip for the trigger cannula resembles the Rubin-Myller inflatable cannula only in that both obturate the cervix by inflation of a balloon within the cervical canal. However, there is a definite difference in the systems used to obtain the gas-tight cervical seal.

The use of the traction tenaculum with the trigger mechanism has been incorporated as an integral part of the cannula for obtaining gas-tight obturation of the cervix with all tips. The tenaculum is thus employed to aid in passing the balloon into the cervical canal, to inflate the balloon, and to maintain it in a self-retaining manner in the large, lacerated cervix that defies obturation by other means. Sealing of the internal os is also made possible with the tenaculum in a self-retaining manner. Furthermore, the inflatable tip is round and of the same width and dimension as the other tips, while the Rubin-Myller cannula has a flat, tapering shaft. The inflatable tip also employs a shorter balloon with provision to use a rubber acorn and stop collar alternately or in conjunction.

Since we both agree that leakage is one of the main sources of error in performing the Rubin Test, I am sure that Dr. Myller will be pleased to know that his fears of an "additional connection between the trigger cannula and its multiple tips as a cause of leakage were carefully considered and tested. The maximal carbon dioxide pressure of 200 mm. Hg considered safe for the Rubin test is comparatively low for the effective, though simple, Luer-Lok device used to connect the tips to the handle by a turn. A wide margin of safety has been allowed against leakage of gas or contrast medium.

A simple under-water test as described in the instruction book provided with the cannula should prove convincing. Far more important as a source of error in the Rubin test is the cervical seal.

If the "trigger idea" was "utilized" by the German manufacturer Windler "as far back as twenty years ago," then it seems strange that after careful search no reference could be found.

The trigger cannula outfit was developed to utilize known methods of obturation and cannulization, to refine our techniques, and further to stimulate invention in the field.

EDWARD KAHN, M.D.

1 WEST 81ST STREET
NEW YORK 24, N. Y.
FEB. 5, 1951

Necrology

HARRY STURGEON CROSSEN, M.D., F.A.C.S., author, teacher, and clinician, died March 10, 1951, at his home in St. Louis after a prolonged illness, at the age of 82, from a cerebral hemorrhage. Born in Iowa in 1869, Dr. Crossen graduated from the Medical Department of Washington University in 1892, with which he became associated in 1899 in the gynecological service. Later he was made a clinical professor and acted in this capacity from 1921 to 1935. He was also gynecologist to Barnes Hospital, St. Luke's Hospital, and the St. Louis Maternity Hospital. He was the author of several well-known textbooks, among them *Diseases of Women* (1907) and *Operative Gynecology* (1915), which are still active, having been revised through many editions. Dr. Crossen also served on the Advisory Editorial Staff of the JOURNAL for many years until his retirement from active practice.